SURGICAL
PATHOLOGY

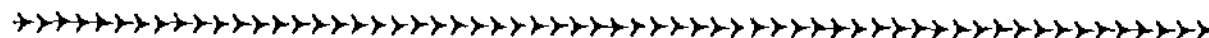


SURGICAL PATHOLOGY



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With 1114 Illustrations
SECOND EDITION

ST. LOUIS
THE C. V. MOSBY COMPANY
1959

SECOND EDITION

Previous edition copyrighted 1953

Printed in the United States of America

Library of Congress Catalog Card Number 59 5467

DISTRIBUTED IN GREAT BRITAIN

BY HENRY KIMPTON, LONDON

To

ARTHUR PURDY STOUT

A good friend a wise counselor and the best surgical pathologist I know

PREFACE TO SECOND EDITION

This second edition has been entirely revised new illustrations have been added and the references brought up to date.

My colleague Dr Harvey R Butcher Jr Associate Professor of Surgery at Washington University has conscientiously edited the entire revision with me and has written the section on Wound Healing and the chapter on Vessels. Numerous books have been written on surgical pathology—most of these by pathologists, a few by surgeons To our knowledge this is the first time a pathologist and a surgeon have collaborated on such a book—an endeavor which we hope will lead to a better understanding of this branch of pathology Clinical pathologic correlation has been strengthened and disease processes as they affect the living patient have been clarified

Because of the untimely death of Dr Zola K. Cooper, her section on Nonneoplastic Conditions of the Skin has been revised by my former assistant Dr Robert Ogilvie now pathologist to St Luke's Hospital in St. Louis. Dr David E. Smith, Professor of Pathology at the University of Virginia has completely rewritten his chapter on the Central Nervous System. Dr L. E. Zimmerman Chief of the Department of Ophthalmology at the Armed Forces Institute of Pathology has written a chapter on the Surgical Pathology of the Eyes and Ocular Adnexa.

My associate, Dr Harlan J Spjut, has given willingly of his time and advice in the preparation of this edition and for this I am deeply grateful. Again I want to thank Mr Cramer Lewis for his continued cooperation and the technical excellence of the illustrations.

LAUREN V ACKERMAN

PREFACE TO FIRST EDITION

This book can be only an introduction to the vast field of surgical pathology the pathology of the living It does not pretend to replace in any way the text books of general pathology, its purpose being merely to supplement them assuming that the reader has a background in or access to those texts The contents are not as complete as they might be because emphasis has been placed on the common rather than the rare lesions and are to a great extent based on the author's personal experiences

This book has been written for the medical student as well as for those physicians who are daily intimately concerned with surgical pathology This must of necessity include not only the surgeon and the pathologist but also those physicians in other fields who are affected by its decisions such as the radiologist and the internist Gross pathology has been stressed throughout with an attempt to correlate the gross findings with the clinical observations The many illustrations have been selected as typical of the various surgical conditions although in a few instances the author has been unable to resist showing some of the more interesting rare lesions he has encountered Concluding each chapter there is a bibliography listing those references which are not only relatively recent and readily available but also those which will lead the reader to a more detailed knowledge of the subject.

Dr Zola K. Cooper Assistant Professor of Pathology and Surgical Pathology has written one of the sections on Skin and Dr David E Smith Assistant Professor of Pathology and Surgical Pathology, has written the chapter on Central Nervous System. Both of these members of the Department are particularly well qualified for their respective roles because of their background and present responsibilities in these fields Their efforts on my behalf are most gratefully acknowledged.

Many members of the Surgical Staff at Barnes Hospital have given much help both knowingly and unwittingly I am particularly grateful to Dr Charles L. Eckert Associate Professor of Surgery, for letting me bother him rather constantly with my questions and for giving freely of his experience. Dr Richard Johnson, who succeeded me as Pathologist at the Ellis Fischel State Cancer Hospital, agreeably made available all the material there and Dr Franz Leidler Pathologist at the Veterans Hospital, has been most cooperative

Thanks must be given to Dr H. R. McCarroll, Assistant Professor of Orthopedics, for constructively criticizing the chapter on Bone and Joint and to Dr C A. Waldron for helping me with the chapters related to the Oral Cavity Among other faculty friends and colleagues who were especially helpful, I would like to mention Dr Carl E Lischer Dr Eugene M Bricker Dr Heinz Haffner Dr Thomas H. Burford, Dr Carl A. Moyer, Dr Evarts A. Graham, Dr Robert Elman, Dr Edward H. Reinhard Dr J Albert Key Dr Glover H Copher, Dr Margaret G Smith and Dr Robert A Moore.

Mr Cramer K. Lewis, of our Department of Illustration has been very patient with my demands, and his efforts and skill have been invaluable. Miss Marion Murphy in charge of our Medical Library and her associates gave untiringly of their time.

Because of recent advances in anesthesia, antibiotics and pre and post operative care modern surgery permits the radical excision of portions or all of various organs There is a need today for contemplative surgeons, men with a rich background in the fundamental sciences, whether chemistry physiology or pathology The modern surgeon should not ask himself 'Can I get away with this operation?" but rather What does the future hold for this patient?" It is hoped that this book may contribute in some small fashion toward the acquisition of this attitude.

LAUREN V ACKERMAN

St Louis Mo

CONTENTS

Chapter 9

Chapter 10

Chapter 11

Chapter 17

Chapter 18

SURGICAL
PATHOLOGY

Chapter 1

INTRODUCTION

SURGICAL PATHOLOGY AND THE SURGICAL PATHOLOGIST

The Department of Pathology in large medical centers should be divided so that a Department of Surgical Pathology exists closely affiliated with surgery. In the past the diagnosis of tissue removed from a living patient often was delegated to a resident and reports emanating from the Department of Pathology not only were delayed but often indicated only whether the tissue was benign or malignant. These circumstances sometimes forced clinicians to direct some branch of surgical pathology; under these conditions the clinician's diagnoses and recommendations were better than those of the experienced uninterested pathologist. Although it is mandatory for the clinician to have some knowledge of surgical pathology, it is difficult, if not impossible, to be both a competent clinician and a skillful pathologist. Nor is it rational for the surgical pathologist to believe himself capable of doing radical mastectomies as a sideline. There are exceptional persons who are not trained pathologists but who have made fundamental contributions to pathology in their respective fields of interest. However, the most profitable arrangement is to have an experienced pathologist with a clinical background working with clinicians interested in pathology.

Surgical pathology implies surgery, but actually the surgical pathologist is closely affiliated with all branches of medicine. A peripheral lymph node may show unexpected lymphosarcoma and resolve a difficult diagnosis for the internist. An aspiration biopsy of the liver may clarify a diagnostic problem for the pediatrician. Close cooperation with the Department of Radiology is essential.

The surgical pathologist has the unique opportunity of bridging the gap between the beginning of disease and its end stages and he should take advantage of this circumstance. He can do this only after a solid foundation of study at the autopsy table where the ravages of cancer, tuberculosis, ulcerative colitis, and other diseases are all too clear. With this background, he can then correlate the initial

stages of disease seen in specimens from living patients in the surgical pathology laboratory With this objective in mind, the student may make many fundamental contributions to knowledge with the integration of clinical findings pathologic anatomy is still a living science Only by understanding the pathology of disease as a whole can the pathologic process affecting a given organ be understood This is the main reason a clinician cannot hope to deal adequately with some small branch of surgical pathology Disease does not cooperate by remaining neatly con fined to an anatomic system

The surgical pathologist must not only know his own field thoroughly but must have a rich background of clinical medicine He should be in a position to advise the clinician about the biopsy or excised material that he receives. It is not sufficient for him to be able to say whether a lesion is benign or malignant he must be able to tell the surgeon the extent of the disease, the adequacy of the ex cision and other pertinent information. He can do this only if all clinical and laboratory data are supplied him by the clinician. There are still pathologists who pride themselves on being able to render an opinion and make recommendations for treatment without clinical information The pathologist makes enough errors with out trying to be dramatic.

The surgical pathologist by the very nature of the material submitted to him makes mistakes. He sees the earliest subtle and sometimes bewildering changes in Hodgkin's disease He may very well not recognize that the minimal granu lomatous response in a lymph node is really a peripheral manifestation of histoplasmosis. The surgical pathologist must continue to haunt the postmortem table, for there his diagnoses are confirmed or his errors are made painfully clear The necessity of follow up on the patient in whom the diagnosis is not certain is manda tory Time is often a better diagnostician

The surgeon we choose to operate has not only technical dexterity (a fairly common commodity) but, more important, good *judgment* and a personal concern for his patient's welfare. The surgeon with a prepared mind and a clear concept of the pathology of disease invariably is the one with good judgment. Without this background of knowledge, the surgeon will not recognize specific pathologic al terations at operation, nor will he have a clear concept of the limitations of his knowledge and therefore will not know when to call the pathologist to help him Without this basic knowledge, he may improve his technical ability but never his judgment. You might say that with time his ignorance is refined rather than his knowledge broadened.

Although the study of radiology deals with shadows and the study of pathology with substance the correlation of those shadows with the gross substance strengthens the diagnostic skill of the radiologist, explains errors in radiologic interpretation and instills humility rather than dogmatism The radiotherapist, too can learn much from the study of surgical pathology particularly the effects of irradiation on normal tissue and radiosensitive neoplasms Furthermore explanations for the success or failure of irradiation therapy may become apparent by the study of surgical speci mens.

BIOPSY

The interpretation of a biopsy is one of the most important duties of the surgical pathologist. Certain generalizations must be mentioned even though they are obvious. Material obtained by cautery is usually unsatisfactory for biopsy because the cautery chars and distorts the tissue and prevents clear staining. If the tumor shows a central ulceration removal of a small biopsy from the center may show only necrosis and inflammation. The biopsy should be taken with a cold knife from the margin of the ulcer and should include both normal and ulcerated tissue. In a mass of lymph nodes a deep seated node may be of diagnostic value while a superficial node is not. We have seen bone biopsies taken near the lesion but not through it. *The pathologist cannot make a diagnosis of a disease from material which is not representative.* The surgeon should be equipped with the proper instruments to obtain the best possible biopsy whether it be from the esophagus bronchus nasopharynx endometrium or even stomach.

The size of the biopsy may range from the smallest wisp of tissue to a large excision. It is imperative that the small biopsies be quickly placed in good fixative. Ten per cent formalin is not the best but is the one most commonly used. Probably Bouin's solution is a better general fixative. If lymph nodes or small biopsies of bone marrow are to be studied they should be placed immediately in Zenker's acetic acid. It is unfortunate if tissue which has been carefully and tediously obtained by the surgeon is mishandled allowed to dry or poorly fixed.

Aspiration Biopsy

There are *two ways of handling* an aspiration biopsy. *The material obtained* is either smeared on a slide or placed in a fixative and sectioned as a small tissue biopsy. While a diagnosis may be made on smeared material, the skill and effort entailed in making a diagnosis by smear are great. We therefore recommend placing the material in fixative and cutting it as a small biopsy because under these conditions the architecture is maintained. If the biopsy is positive the diagnosis is assuredly accurate and surgery can be undertaken without delay. If the diagnosis is negative or the material is insufficient, cancer may still be present. The value of a negative biopsy depends to a great extent upon the skill of the person taking the biopsy (Meatheringham). The merits and indications for incisional and aspiration biopsy are more fully discussed in each chapter.

Frozen Section

Frozen section technique is a procedure of great value to the surgeon. The only reason for frozen section is *to make a therapeutic decision* (Ackerman). A frozen section should be accurate rapid and reliable. We believe that the responsibility of frozen section diagnosis should be that of a senior pathologist and such a man should be experienced, conservative in attitude and above all must have judgment. We do not favor using the pathologist as a technician to satisfy the *surgeon's intellectual curiosity* or to *prove that the pathologist is in the hospital*. Frozen section diagnosis should not be a method used routinely in every specimen removed at the operating table but should be reserved for those instances in which

a therapy will be effected. The indications and limitations of this method of diagnosis vary from organ to organ and have been detailed in the respective chapters. Although the pathologist must be conservative he must not be so conservative as not to make some decision otherwise his value to the surgeon is diminished tremendously In as much as he is using his knowledge to the limit rare errors may be made (Table 1) Frozen section diagnosis demands of a pathologist a well balanced clinical background coupled with skillful interpretation and an awareness of the limitations of the method. The pathologist should enter the operating room thoroughly briefed on the clinical history of the patient and should consult with the surgeon as to the best area to biopsy He must then have skill in selecting from the removed material the piece to be frozen and stained. Various stains can be used, a polychromatic stain (methylene blue) is used to bring out epithelial cells and connective tissue differentially In cancer there are only three possible diagnoses positive for cancer negative for cancer or no diagnosis made.

TABLE 1 FROZEN SECTION DIAGNOSIS IN 1 269 CASES

ORGAN	NO OF FROZEN SECTIONS	FALSE POSITIVE	FALSE NEGATIVE	TUMORS	TUMORS MALIGNANT	TUMORS BENIGN
Breast	440	0	4	263	205	58
Soft tissue	99	2	0	69	57	12
Thyroid	63	0	2	19	12	7
Prostate	21	0	3	10	10	0
Liver	42	0	0	26	25	1
Bowel	70	0	1	38	24	14
Lymph nodes	143	0	3	63	63	0
Lung	143	2	1	89	84	5
Pancreas and periampullary region	68	0	6	49	46	3
Stomach	58	0	1	24	18	6
Skin	35	0	1	22	22	0
Oral cavity	22	0	0	12	11	1
Miscellaneous	65	0	0	43	34	9
Total	1 269	4 (0.3%)	22 (1.7%)	727 (57.3%)	611 (48.1%)	116 (9.1%)

Over-all Accuracy—98%
Over-all Error—2%

At times more than one frozen section is required The diagnosis is most important because upon it rests the decision to remove a breast amputate a leg remove a lung or to terminate the operation It is evident that a surgeon with only a slight knowledge of pathology is not equipped to interpret a frozen section nor are general pathologists with little clinical knowledge qualified to undertake them.

Exfoliative Cytology

Exfoliative cytology has become extremely popular in the United States, and today where many Departments of Pathology use this technique the diagnosis of cytologic material usually is based on the apparent presence or absence of cancer cells. The decision is of course of great significance in some instances the method has become discredited because poorly trained pathologists gynecologists, and technicians have been handling the material and making definitive diagnoses which

ove to be incorrect The cytologist will make a certain number of false nega e diagnoses depending on the source of the material but false positives should actically never occur for they will in themselves invalidate the method

We have made it our policy to render the following reports

1 The material is insufficient for diagnosis
2 No cancer cells are seen
3 There are ome cells present of which we are not certain (This simply means that the cells may or may not be cancer cells and we would like further material to study)
4 We believe that cancer cells are present

nder most circumstances we feel that a determined effort must be made to sub antiate the diagnosis by a conventional biopsy procedure before decisive treat ent is carried out For instance if a cytologic diagnosis of cancer is obtained om a cervical smear irradiation or surgical treatment should not be started until positive formal biopsy is at hand Of course exceptions to this rule occur A tient may have a shadow in the right lung field and a negative bronchoscopic opsy the sputum shows cancer cells We believe this finding is reliable enough to commend thoracotomy with lobectomy or pneumonectomy without benefit of ozen section (see Lung p 207) In this instance the weight of a positive cytologic agnosis is added to the clinical and radiologic evidence of carcinoma and helps ake the decision to resect the lung

Exfoliative cytology is of little value for lesions which are readily accessible incisional biopsy such as the skin or oral cavity Neither does it seem advisable use this time-consuming method as a screening procedure for asymptomatic atients except under special circumstances It is logical to screen cytologically lected groups of patients in whom the statistical chance of finding a cancer is gh enough to warrant the time and expense This might include patients with ernicious anemia and those over 40 with achlorhydria in this group there is a eightened chance of the patient having cancer of the stomach and gastric cytology ould be of value There may come a time when it will be technically feasible screen all women over 25 years of age for cancer of the cervix and endometrium reliminary work in this area of investigation has yielded encouraging results (see emale Reproductive System p 602) It must be remembered however that nly a positive result has value and a negative finding does not necessarily indicate hat cancer is not present The indications and limitations of this method are iscussed further in the individual chapters.

one Marrow Biopsy

Bone marrow biopsy is a definite adjunct to diagnosis of obscure anemias and ematologic abnormalities Some hematologists rely on aspiration and staining y Wright's stain. However, this has the disadvantage that no pattern is seen nd pooling of the material occurs Incisional biopsy may be the only means of ecuring material from patients with myelofibrosis or myelosclerosis. We firmly gree with Custer that the combination of stained sections and Wright's smears ive the most information On numerous occasions these procedures have given

diagnoses not possible by using either the smear or biopsy alone. At the time of aspiration of the bone marrow there are often fragments of marrow These fragments should be carefully placed on filter paper and placed in Zenker s acetic acid Eosin methylene blue is an excellent stain for nuclear detail. We have found unexpected histoplasmosis, metastatic cancer, and leukemia in such sections. A detailed review of the bone marrow findings is not warranted in a book of this type (see Custer)

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Chapter 2

SKIN

NONNEOPLASTIC CONDITIONS

Zola K. Cooper, Ph.D.,† and Robert Ogilvie, M.D.

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†Deceased.

Inflammatory Nodular Lesions of the Legs
- Erythema Nodosum
- Erythema Induratum
- Weber-Christian Disease (Relapsing Febrile Nodular Nonsuppurative Panniculitis)

Inflammatory Diseases Resulting in Vesicle Formation
- Eczema
- Dermatitis Herpetiformis
- Pemphigoid (Bullous Pemphigoid)
- Pemphigus

Diseases Caused by Bacteria
- Hidradenitis Suppurativa
- Tuberculosis

Diseases Caused by Fungi
- North American Blastomycosis
- Chromoblastomycosis (Chromomycosis)

"Insect" Bites

Granulomas of Unknown Etiology
- Sarcoid
- Lichen Nitidus

Diseases of Metabolism
- Bromoderma
- Necrobiosis Lipoidica Diabeticorum
- Xanthoma
- Juvenile Xanthogranuloma (Nevoxanthoendothelioma)

SKIN BIOPSY

Dermal pathology differs from other branches of surgical pathology in that biopsy specimens make up almost all of the material to be examined These small pieces of skin taken with the hope that they will help with the diagnosis of the patient's skin disorder are rarely over 1 cm. in greatest dimension and may be much smaller particularly if they have been removed from the face They may be elliptical in shape when they are taken with a scalpel or round when removed with a biopsy punch. A piece of skin which is 6 to 8 mm. in diameter and includes the full thickness of the skin and some of the subcutaneous fat is usually adequate for diagnosis in nonneoplastic conditions and in some instances even smaller specimens may be satisfactory Generally excisional biopsies are preferable to punch biopsies in small tumors and multiple marginal wedge biopsy to include normal skin and tumor is preferred for diagnostic evaluation of large skin tumors. Specimens should not be taken with cautery or electric current for the distortion of the cells may be so great as to make diagnosis impossible.

As a rule, with the exception of the tumors, very little can be seen on gross examination of the biopsy specimen. In generalized skin diseases the gross pathologic changes must be seen on the patient and an adequate site for biopsy selected. In the dermatoses avoidance of areas which have been severely scratched or otherwise irritated is advisable because of the alterations of the histology thereby produced which often make proper evaluation difficult. A well-developed lesion is usually the most satisfactory for an early lesion may not show a definitive microscopic picture, and a late lesion, which has become secondarily infected or crusted

which is involuting may be misleading. For example, in vesicular lesions it is important to obtain an intact vesicle, for one that has ruptured may show nothing but a nonspecific superficial ulcer. In lesions which exhibit a variable gross appearance from area to area, biopsy of several selected areas is often fruitful. In mycosis fungoides, for instance, an erythematous area may be nondiagnostic while an adjacent or distant more indurated plaque or nodule may be diagnostic.

Better microscopic sections will be obtained if the specimen is flattened on a small piece of white soft blotting paper before it is placed in the fixative. If the cut surface is pressed gently against the blotter, the specimen will usually adhere. When the specimen and blotter are dropped into fixative, the piece of skin will not curl, and complete sections can be obtained. The blotter is removed, of course, during the process of dehydration of the tissue, since after fixation the specimen will remain straight.

With the exception of the tumors, it is usually preferable not to cut a small specimen of skin in half grossly, as is usually done with other surgical specimens. Even if both halves are sectioned, in squaring up the paraffin blocks to obtain a ribbon, significant portions of the tissue may be lost, and two pieces instead of one double this hazard.

It is important in studying even a small specimen of skin to examine a number of sections, since significant changes may not be found uniformly throughout the block of tissue. For example, microscopic vesicles may be missed if only one or two sections are examined. As a routine procedure it is helpful to have six or seven sections mounted on each slide and the block cut at three or more different levels. In this way a total of approximately twenty sections are examined which have been obtained from different portions of the lesion or lesions included in the specimen. At times a small vesicopustule may be present in one section and absent in another section less than 0.5 mm. away (Figs. 1 and 2). It may occasionally be necessary to cut through the entire block, obtaining representative sections at various levels before adequate evaluation can be achieved.

Even with the utmost care in preparing the specimens, one is forced to admit that dermal pathology has its limitations. Although the patient may present definite clinical lesions, sometimes all that can be seen microscopically is a nonspecific inflammatory reaction. Parapsoriasis, urticaria, and some of the drug eruptions usually are not diagnostic *microscopically*. Often in diseases which have a characteristic histopathologic picture an individual case may be only suggestive. However, in spite of these difficulties, a careful attempt to separate various entities should be made, *for there are many* skin diseases that have a characteristic microscopic picture. *In addition, even* though a specific histologic diagnosis may not be possible in a given case, certain entities of differential diagnostic significance may be effectively ruled out; this may be of considerable assistance, particularly to the dermatologist.

Nowhere in pathology is it more important to obtain clinical information for correlation with tissue morphology than in the complexities of skin pathology. Those who would adhere to pure morphology without such aid are both doing disservice to the patient and truly practicing pathology in vacuo. The all-encom

passing diagnosis of chronic inflammation which was probably as obvious to the clinician who obtained the biopsy specimen as it is to the pathologist, should be used only as a last resort.



Fig. 1 —A vericopustule produced by the bite of an arachnid, the grain mite. (×200) (W U neg 52 2977)

Fig 2 —Section from the same block shown in Fig 1 taken less than 0 5 mm. away (×200) (W U neg 52 2978)

GENERAL CONSIDERATIONS

The Epidermis and Pathologic Processes Occurring Within It

The skin is made up of the epidermis and the dermis. Over most of the body in young persons the junction of these two layers is irregular The interdigitations

of the epidermis with the dermis which are usually called rete ridges are not fingerlike projections or pegs but are the lateral walls of the meshes of a net. The proximal side of the epidermis when viewed as a sheet resembles a honeycomb. Into each space in this net the dermis projects as a dermal papilla. With advancing age the epidermis tends to become atrophic and this honeycomb like structure is reduced in depth (Figs 3 4 5 and 6). In extreme old age the epidermis becomes almost a flat sheet and the junction between epidermis and dermis in sections appears as almost a straight line. This is one of the normally occurring changes with age that must be taken into account when a pathologic specimen is examined. In addition to age changes regional variation should be kept in mind.

The epidermis is composed of the basal layer the spinous or prickle layer the granular layer, and the horny layer. On the palms and soles an additional layer is present between the granular layer and the horny layer the stratum lucidum. Pathologic changes may occur in any one or any combination of these layers.

The horny layer or stratum corneum is composed of keratinized flattened cells which have lost their nuclei. The width of this layer normally varies in different portions of the body but when it becomes pathologically thickened this process is called *hyperkeratosis*. When there is a defect in keratinization the nuclei are retained in the horny layer and this pathologic change is known as *parakeratosis*. Sometimes the whole horny layer will show parakeratosis as in psoriasis; sometimes there will be alternate areas of parakeratosis and hyperkeratosis as in pityriasis rubra pilaris (Fig 7). The granular layer is present under areas of hyperkeratosis but is absent under areas of parakeratosis.

The rete malpighii which includes the spinous or prickle layer and the basal layer may also undergo a number of pathologic changes. In diseases in which the epidermis becomes atrophic, for example in scleroderma the rete ridges are obliterated and the spinous layer may be reduced to three or four cell layers in thickness (Fig 27). In other diseases the rete malpighii is thickened and this process is known as *acanthosis*. Two types of acanthosis can occur regular and irregular. In regular acanthosis the rete ridges retain their usual contour and are increased to approximately equal length. In irregular acanthosis the rete malpighii has proliferated for unequal distances into the dermis. Sometimes as in the fungous diseases, this irregular thickening of the epidermis becomes so pronounced that it mimics carcinoma and is spoken of as *pseudoepitheliomatous hyperplasia* (Fig 45).

Sometimes the surface of the skin has an undulating contour that is produced by irregular upgrowths of the epidermis which is usually acanthotic. These upgrowths overlie elongated dermal papillae. This change is described as *papillomatosis* and an example of this process is seen in acanthosis nigricans (Fig 22).

Edema in the epidermis may occur within cells *(intracellular edema)* or between cells of the spinous layer *(spongiosis* or *intercellular edema)*. In moderate intercellular edema the intercellular bridges are very conspicuous and each cell is clearly outlined as in contact dermatitis (Fig 8). When the edema becomes more pronounced small vacuoles or vesicles are found between the epidermal cells and the process is termed *spongiotic vesicle formation*. The latter is one of the characteristic features of the eczemas. Sometimes edema in the epidermis may be

almost entirely limited to the basal layer so that the usually sharp outline between the epidermis and the dermis is lost and small vacuoles may appear. This is known as *liquefaction degeneration* of the basal layer and occurs in lupus erythematosus (Fig 34) and in lichen planus. In addition to the spongiotic vesicle characteristic

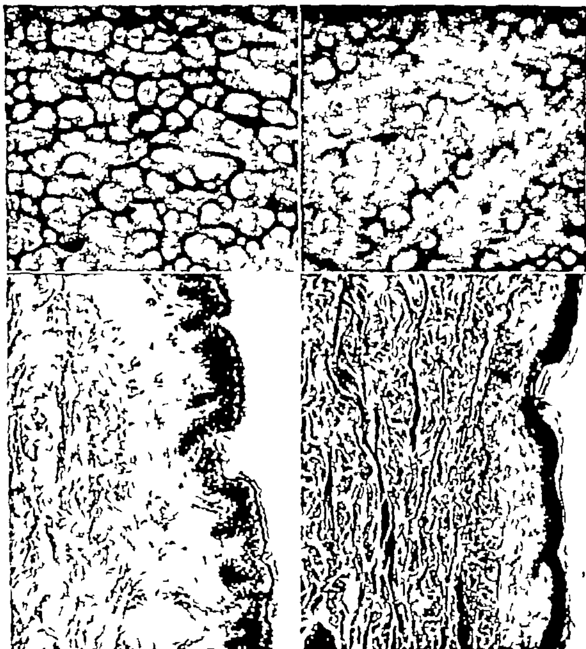


Fig 3.—Epidermis from the thigh of a 29-year-old man viewed from the proximal surface. The rete is well developed. (W U neg. 51 732.)

Fig. 4.—Epidermis from the thigh of a 68-year-old man. The rete is almost obliterated. Clear interlacing lines are creases or wrinkles in the skin which are of microscopic dimensions. Atrophy is most pronounced in these creases. (W U neg 51 731.)

Fig 5.—Section of skin from the abdomen of a woman 35 years of age. (×150.)

Fig 6.—Section of skin from the abdomen of a woman 69 years of age. The epidermis is atrophic and the rete ridges are almost obliterated. The collagen fibers of the dermis are thickened and somewhat sclerotic. (×150.)

of eczema other types of vesicle formation are encountered Individual cells may become swollen by intracytoplasmic edema and lose their intercellular bridges *(ballooning degeneration)* the balloon cells become separated from one another cytoplasmic disruption often occurs and a vesicle is formed In *reticular degeneration* there is coalescence of groups of edematous cells with partial cytoplasmic disintegration and vesicle formation, residual columns of more intact cells or cell membranes traverse the vesicle to produce a reticulated or multilocular structure



Fig 7—Portion of the epidermis in pityriasis rubra pilaris showing alternate areas of hyperkeratosis and parakeratosis. Granular layer is present under areas of hyperkeratosis and absent under areas of parakeratosis. (×200) (W U neg 52-4403)

The vesicles of the cutaneous viral diseases such as herpes varicella and variola are the result of ballooning degeneration combined with reticular degeneration (Figs. 9 and 10) The so-called pressure vesicle" an example of which is found in dermatitis herpetiformis, is thought to be formed by an inrush of fluid which often creates enough pressure to separate the epidermis from the dermis or to separate the layers of epidermal cells (Fig 11) *Acantholysis* is a degenerative process involving the epidermal cells and resulting in loss of intercellular bridges and cellular cohesiveness with subsequent vesicle formation. Such a process is characteristic of pemphigus vulgaris.

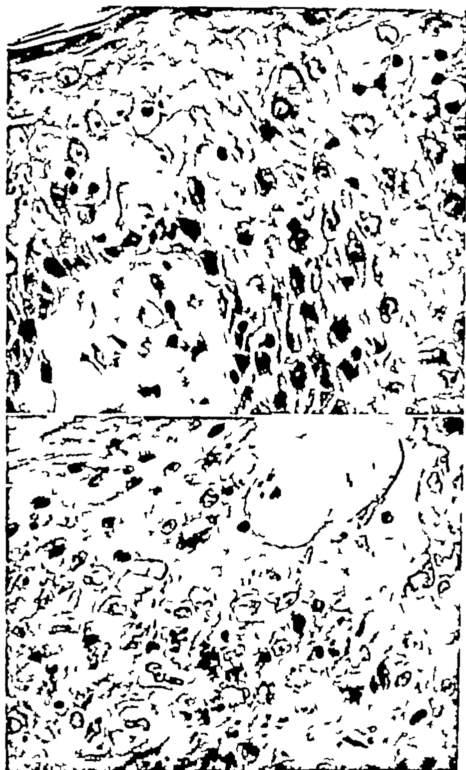


Fig 8.—Epidermis in contact dermatitis showing pronounced intercellular edema. ×750) (W U neg 52-4501)

Fig 9.—Epidermis in smallpox showing ballooning degeneration and reticular degeneration (×750) (W U neg 52-4502)





Fig 10 —Vesicle in chicken pox the result of ballooning degeneration and reticular degeneration. (×120) (W U neg 52-4503)

Fig 11 —A pressure vesicle in dermatitis herpetiformis.

Vesicles may be formed within the epidermis or at the junction of the dermis and epidermis. This localization together with the type of vesicle (spongiotic, acantholytic, pressure, etc.) are of considerable importance in histologically differentiating the various bullous diseases.

In normal skin the basal layer has one characteristic which distinguishes it from the other layers of the epidermis. Its cells usually contain most of the melanin of the epidermis, and scattered among the basal cells are the melanoblasts or pigment producing cells. When sections of skin are treated with levorotatory dihydroxyphenylalanine (dopa) the melanoblasts darken and their dendrites can be seen clearly (Fig 12). This reaction was formerly thought to be due to the presence in these cells of an enzyme, dopa-oxidase, which reacted with dihydroxyphenylalanine to produce melanin. It was postulated that in the human body a dopa like substance was brought to the melanoblasts by the blood stream. Fitzpatrick has shown that tyrosinase is present in human skin. Tyrosine a stable amino acid, is probably the physiologic precursor of melanin. The production of

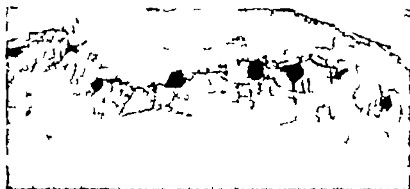


Fig 12.—A dopa reaction showing dopa positive dendritic melanoblasts in the basal layer of human epidermis. (×400) (W U neg 52 4402.)

melanin in the dendritic cells or melanoblasts is believed to be the result of a tyrosine tyrosinase reaction. Dendritic cells are present in comparable numbers in albinic, vitiliginous and normal skins but the difference in the amount of melanin present in different skins is due to a functional inhibition of the tyrosine tyrosinase reaction. In sections stained with hematoxylin and eosin clear cells are seen in the basal layer. They are thought by most workers to be melanoblasts or dendritic cells (cellules claires of Masson). The chromatophores found in the upper part of the dermis do not produce melanin but merely carry it. In other words, they contain no enzyme and are not dopa positive.

Barr first reported the existence of a chromatin body occurring adjacent to the nucleolus within the nerve cells of the cat. Such chromatin masses were subsequently encountered in many different tissues in man and were found to be related to the sex of the individual, being well developed and commonly seen in nuclei of females and infrequently seen in males (Fig 13). In cells other than neurones, this sex chromatin body appears as a planoconvex hematoxylin and Feulgen positive mass within the nucleus impinging against the nuclear membrane. Due to the ready availability and ease of obtaining specimens skin biopsy and subse

quently oral mucosal smears have been utilized in the determination of chromosomal sex. Such procedures have been of diagnostic aid in evaluation of hermaphroditism and gonadal dysgenesis (Grumbach) Furthermore, studies of sex chromatin within tumor cells have been of great interest in the problem of tumor histogenesis as illustrated by the finding of female type nuclei in some teratomas of the testis and mediastinum (Cruikshank Hunter)



Fig 13 —Photomicrograph demonstrating the sex chromatin bodies impinging against the nuclear membrane The presence of these bodies indicates that the biopsy came from a female (×1000) (W U neg 55-6045)

The Dermis

The dermis or corium is made up of connective tissue which is composed largely of collagen bundles among which are interwoven the elastic fibers. The dermis may be divided into two regions the upper or outer narrower zone the papillary layer and the lower wider zone, the reticular layer These layers are not as clearly demarcated as are the layers of the epidermis but merge into one another The collagen fibers of the papillary layer are fine and are not arranged parallel to the surface of the skin as are those of the reticular layer The elastic fibers are found throughout the dermis between the collagen bundles. They form by their anastomosing branches a network about the collagen bundles

On the exposed portion of the body changes occur in the dermis with age In persons who have been exposed continuously to the weather such as farmers these degenerative changes appear sometimes as early as the third or fourth decade and they are more pronounced. In skin taken from exposed portions of the body in older persons the fibers of the papillary layer have a basophilic tint in sections stained with hematoxylin-eosin The collagen fibers seem to be clumped this change in their structure and staining reaction has been called basophilic degeneration. A stain for elastic tissue shows that in these areas the elastic fibers are also

Fig 14—Skin from the cheek of a 74 year-old man (Verhoeff's elastic tissue stain) Elastic tissue fibers in the upper part of the dermis show clumping and degeneration. (×160) (W U neg 51 2180)



Fig 15—Skin appendages sebaceous gland lanugo hair follicle, sweat gland.

swollen clumped and fragmented (Fig 14) They, too are slightly basophilic when stained with hematoxylin-eosin These changes are usually limited to the upper third of the dermis, but many extend more deeply and are referred to as *senile elastosis*

The skin is a relatively vascular organ but its blood supply is not so great as for example that of muscle Two large vascular plexuses are present in the skin, one in the deeper portion of the dermis and one in the mid-dermis, from which numerous small branches arise and extend into the dermal papillae as terminal capillary loops In the subcutaneous fat the walls of the arterioles have three layers adventitia, media and intima but in the dermis proper most of the vessels are capillaries lined by a single row of endothelial cells However in the deeper portion of the dermis media and adventitia can be distinguished in some of the arterioles Farber has shown that there tends to be an increase in thickness of cutaneous vessel walls with age even in persons whose blood pressure is normal In some of the inflammatory diseases of the skin the distribution of the cellular in filtrate may be determined by the location of the vascular plexuses

There are also two lymphatic plexuses in the skin one at the junction of the dermis and the subcutaneous tissue and the other just below the papillary layer from which loops extend into the dermal papillae The lining of the lymph vessels, like the capillaries is made up of a single row of endothelial cells.

Both medullated and nonmedullated nerves are present in the skin as well as a number of interesting specialized nerve endings such as the pacinian corpus cles and the Wagner Meissner corpuscle however, in routine diagnosis of skin diseases changes in the nerves play little part

Skin Appendages

The skin appendages are the hair follicles the sebaceous glands and the sweat glands (Fig 15) Embryologically all of these structures are derived from the epidermis with the exception of certain parts of the hair follicle which are of con nective tissue origin From the standpoint of pathology, the skin appendages are important in two ways first, because certain diseases are limited to them. Both benign and malignant tumors may arise from any of the appendages. Each type of appendage may be the site of certain inflammatory diseases as for example hidradenitis suppurativa, which is an inflammatory disease of the apocrine sweat glands Second, they are important because changes in them are associated with other diseases which are not diseases of the appendages per se. For example in discoid lupus erythematosus the hair follicles are always distended and plugged with keratin In hemochromatosis the deposition of hemosiderin is most con spicuous about the sweat glands.

SPECIFIC SKIN DISEASES

In the following section on specific skin diseases selection of the material to be presented was difficult because of the great number of diseases in which a biopsy can be helpful. It was decided to limit the material to a few examples in each category in which the microscopic picture is quite exact An attempt was

made to choose lesions on which biopsy specimens might be sent to a general surgical pathology laboratory, and at the same time, to give examples that would illustrate types of reactions that can occur in the skin.

Hypertrophies

In most of the so-called hypertrophies of the skin the epidermis is chiefly affected. The four lesions to be discussed are examples of this kind. Under this category scleroderma and cutis hyperelastica are sometimes included since they may show hypertrophy of the collagen and of the elastic tissue, respectively However these two diseases will be discussed elsewhere.

Verruca (Wart) —Warts are circumscribed lesions which may be single or multiple and can occur anywhere on the skin although they are found most commonly on the hands or feet Clinically they are usually divided into several varieties. *Verruca vulgaris* which is the type most commonly seen on the hands of children, is usually a slightly elevated lesion that has a roughened surface (verrucous) made up of small horny projections. It is often the color of normal skin but may be gray or brown *Verruca plantaris* (plantar wart) occurs on the sole of the foot and often resembles a callosity It is usually quite painful *Verruca plana* is a small smooth slightly elevated lesion which is irregular in shape and is found on the face and dorsa of the hands. Although these clinical varieties present slightly different histologic pictures, they are all thought to be caused by a virus. As early as 1919 Wile produced verrucae on human skin by inoculation of a bacteriologically sterile cell free filtrate obtained from ground-up warts.

Microscopically the epidermis in both verruca vulgaris and in verruca plantaris shows pronounced hyperkeratosis with areas of parakeratosis acanthosis, and papillomatosis (Fig 16) The rete ridges are hyperplastic, and at the edge of the lesion where it adjoins normal skin the rete ridges show a tendency to taper inward toward the center of the lesion as though setting it off from the normal skin In the cells of the spinous layer in many warts cytoplasmic masses are present (Fig 17) In the lower rows of cells these masses are small but they become larger in the cells nearer the surface of the skin, where at times they are almost the size of the nucleus. In the deeper cells of the spinous layer these masses are slightly basophilic, but in the outermost cells they are acidophilic and stain brightly with eosin. Strauss and Blank have also described intranuclear inclusions in these cells Strauss has been able to demonstrate, by means of electron microscope studies crystalline viruslike particles from warts in which cytoplasmic and intranuclear inclusions were present. He believes that these particles are elementary bodies of the virus which is the etiologic agent in these warts. Vacuolation of cells of the granular and spinous layers is usually prominent, and in those cases in which inclusions are not evident, the vacuolation is often diagnostic.

Verruca plana differs from the other two types of verrucae in that there is no papillomatosis. The epidermis shows hyperkeratosis but the stratum corneum has in the words of Waisman, a loosely felted basketweave pattern." The granular layer is thickened and there is acanthosis The cells of both the granular layer and the upper portion of the spinous layer are large and vacuolated.

Fig 16.—Verruca from the palm showing hyperkeratosis acanthosis and papillomatosis. At the border of the lesion rete ridges taper inward. (W U neg 52-4317.)

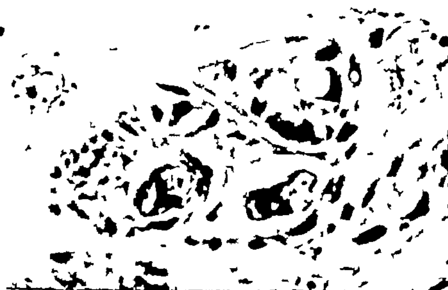


Fig 17.—Verruca. Cells of the spinous layer contain cytoplasmic inclusion. (×1120.) (W U neg 52-4401.)

In none of the types of verrucae are there any striking changes in the dermis. The amount of the inflammatory cellular infiltrate varies with the amount of trauma to which the lesion has been subjected and with the degree of secondary infection that may be present.

Molluscum Contagiosum.—The lesions of molluscum contagiosum vary in size from a few millimeters to a centimeter in diameter They are usually elevated, firm, and waxy white. In a well-developed lesion, cheesy material may be ex

Fig 18.—Molluscum contagiosum (W U neg. 50-6011)



Fig 19—High-power photomicrograph showing the cytoplasmic inclusion bodies in molluscum contagiosum. The inclusion displaces the nucleus to one side of the cell. (W U neg 50-6008.)

pressed from a small opening in the center of the lesion This feature may lead to the erroneous conclusion that the lesion is an epidermal inclusion cyst These lesions are caused by a virus and are usually multiple In a typical case the diagnosis is usually made clinically, but occasionally when only one or two lesions are present, they have been mistaken for basal cell carcinoma by competent clinicians

The histopathologic picture is very characteristic (Fig 18) The lesion is lobulated Each lobule is made up of hyperplastic epidermis which has grown down into the dermis In most of the cells of the spinous layer large cytoplasmic inclusion bodies are present (Fig 19) They are homogeneous or finely granular and eosinophilic. The inclusion body may be as large as 35 microns in diameter and fill the entire cell so that the nucleus is pushed over to the cell wall and appears as a small dark crescent However, some of the epidermal cells keratinize in the normal way, and in the lobules the granular layer is thickened Keratin is present in the center of each lobule and forms a central core for the whole lesion Numerous inclusion bodies are found in this keratin where they are slightly basophilic. The cytoplasmic inclusion bodies of molluscum contagiosum are composed of elementary bodies They can be readily distinguished from those of verruca. The cytoplasmic inclusion bodies of verruca are usually multiple and do not displace the nucleus as does the molluscum body

Darier's Disease (Keratosis Follicularis)—Darier's disease is relatively rare and the etiology is unknown Clinically it is characterized by a rather widespread eruption made up of small papules which are usually covered with a brown crust By coalescence the papules form small verrucous lesions which may eventually cover large portions of the body and occasionally also involve the mucous membranes Histopathologically the lesion is so characteristic that a biopsy will almost always be diagnostic.

Microscopically Darier's disease is characterized by the presence of lacunae in the epidermis In sections they have the appearance of long narrow vesicles that usually occur just above the basal layer (Fig 20) In the surrounding spinous layer and the granular layer, as well as lying free in the lacuna are cells which have homogeneous, eosinophilic cytoplasm and homogeneous basophilic nuclei Darier called them corps ronds (Fig 21) These cells have become partially keratinized and this process is sometimes spoken of as benign dyskeratosis. Also in the lacunae and above the surrounding granular layer are other degenerating cells which are smaller than the corps ronds and have pyknotic, elongated nuclei that resemble the nuclei retained in the horny layer in areas of parakeratosis. These cells Darier called grains The epidermis as a whole shows hyperkeratosis moderate acanthosis, and papillomatosis In the dermis there is usually a moderate inflammatory perivascular, cellular infiltrate. As a result of the papillomatosis and the hyperkeratosis there is keratotic plugging that is not related to the hair follicles Therefore the disease is not limited to the follicles as Darier originally thought, and the term keratosis follicularis is inaccurate

Acanthosis Nigricans.—In acanthosis nigricans the involved skin becomes pigmented and has a brown or deep gray hue. It also becomes roughened and verrucous or papillomatous areas may develop The lesions may occur anywhere on the body and involve large surfaces, but they have a predilection for the folds of



Fig. 20 —Darier's disease showing an intraepidermal lacuna. (×150) (W U neg 52-4320)

Fig. 21 —Darier's disease showing part of the lacuna illustrated in Fig 20 *Corps ronds and grains can be identified within it. (×400) (W U neg 52 4319)*

the skin and are most commonly found in the axilla on the neck in the groin and beneath the breasts They often have a symmetrical distribution

Two types of acanthosis nigricans exist the benign or juvenile form and the malignant or adult form The malignant type is always associated with carcinoma of the viscera and Curth states that in over 90 per cent of the cases the malignant tumor was in the abdomen most frequently in the stomach The relationship between the skin lesions and the malignant lesion of the internal organs is not completely understood Carcinoma never develops from the cutaneous lesions nor are the skin lesions metastases from a visceral carcinoma



Fig 22.—Acanthosis nigricans. Biopsy from the axilla of a patient who at autopsy was shown to have carcinoma of the stomach Epidermis shows hyperkeratosis, papillomatosis areas of acanthosis alternating with areas of atrophy and increased melanin in the basal layer (×100) (W U neg 52-4321)

In the benign or juvenile type of acanthosis nigricans lesions often appear at puberty and are not associated with a malignant tumor Clinically and histologically the two types are similar

The microscopic picture is diagnostic (Fig 22) The epidermis shows hyperkeratosis and pronounced papillomatosis. Areas of slight acanthosis often alternate

with areas of atrophy and the rete ridges are not very regular Melanin in the basal layer is usually increased in amount. Pathologic changes in the dermis are not conspicuous. A slight perivascular lymphocytic infiltrate may be present, and in the papillary portion of the dermis a few chromatophores containing melanin pigment are often found.

Atrophies

Some of the skin diseases in which clinically the skin appears atrophic will microscopically show atrophy of the epidermis only In others both the dermis and the epidermis are atrophic. Lichen sclerosus et atrophicus is an example of the first type and acrodermatitis chronica atrophicans an example of the second.

Lichen Sclerosus et Atrophicus.—The characteristic clinical feature of lichen sclerosus et atrophicus is a polygonal white papule that may be discrete or may be one of a group which have coalesced to form a plaque. On the surface of each papule is a dark plug resembling a small comedo or a tiny depression which is the site of a former plug Later atrophy usually develops giving rise to a parchmentlike wrinkling and greater prominence of the plugs. The lesions may occur anywhere on the body but the trunk, neck, axillae and vulva are most frequently involved. When the lesion is present on the vulva, it is often mistaken clinically for leukoplakia and vulvectomy is advised. Since lichen sclerosus et atrophicus is not known to give rise to malignancy (whereas leukoplakia is considered to be precancerous) differentiation by biopsy is important. To further complicate matters however leukoplakia may at times occur concurrently with lichen sclerosus et atrophicus. Therefore the selection of biopsy site should include thickened or piled up areas as well as atrophic regions. The etiology of the disease is unknown.

Histologically hyperkeratosis is prominent and the openings of the hair follicles and sweat gland ducts are plugged with keratin. There are often indentations in the epidermis filled with keratin which are independent of the skin appendages. Except for this thickened horny layer the other layers of the epidermis are quite atrophic, and the rete ridges are usually almost completely obliterated (Fig 23) In the upper part of the dermis edema is present and may be so pronounced that the epidermis is separated from the dermis by collections of fluid. The collagen bundles in this area show homogenization and edema. In the mid-dermis there is a moderate inflammatory cellular infiltrate made up largely of lymphocytes. There are no obliterative changes in the deeper blood vessels. In its fully developed form the histologic picture is diagnostic and should not be confused with scleroderma, irradiation effect or other lesions producing dermal sclerosis. Kraurosis vulvae is essentially identical histologically to lichen sclerosus et atrophicus of the vulva, and there is considerable question whether retention of the term kraurosis serves any useful purpose.

Another morphologically identical lesion occurs on the penis namely balanitis xerotica obliterans. Laymon accepts this concept of histologic identity but Montgomery believes that the histologic changes of balanitis xerotica obliterans differ from lichen sclerosus et atrophicus by less marked keratotic plugging and by the

presence of obliterative changes in deeper blood vessels The fact that in a number of cases typical extragenital skin lesions of lichen sclerosus et atrophicus have been noted in patients also having typical balanitis xerotica obliterans is additional evidence supporting the above concept



Fig 23—Lichen sclerosus et atrophicus. The epidermis is atrophic but shows hyperkeratosis. Marked edema in the upper dermis with homogenization of the collagen. Cellular infiltrate in the mid-dermis. (W U neg 52 4330)

Acrodermatitis Chronica Atrophicans—Acrodermatitis chronica atrophicans is a relatively rare disease, so biopsies are not frequently encountered in the usual surgical pathology laboratory However the microscopic picture is so striking because of the pronounced atrophy of the entire skin that any discussion of cutaneous atrophy would be incomplete without mentioning this disease.

The lesions are usually limited to the extremities and are bilateral. The skin is freely movable but it is extremely thin and through it the superficial blood vessels are visible. It is red to brown in color and wrinkled so that Montgomery described it as resembling crumpled cigarette paper There is often superficial scaling on the surface of the skin Sometimes fibrous nodules or infiltrated or fibrous bands and plaques occur which are described as pseudosclerodermatous changes.

When sections are examined from a typical lesion the most striking finding is the extreme thinness of the dermis (Fig 24) The entire epidermis, dermis and part of the subcutaneous fat can be viewed under one low power field of the microscope. The epidermis shows moderate hyperkeratosis, but it is otherwise quite atrophic, and the rete ridges are completely obliterated Immediately beneath the epidermis there is a narrow zone of normal or homogenized connective



Fig 24 —Acrodermatitis chronica atrophicans. Epidermis and dermis show pronounced atrophy Sweat glands lie closer to the epidermis than in normal skin because of the atrophy (×100) (W U neg 52-4322.)

tissue, but below this a band of cellular infiltrate composed mostly of lymphocytes is present. Later this cellular infiltrate may become inconspicuous or absent. The collagen bundles are decreased in thickness and they are slightly separated by edema. The hair follicles and sebaceous glands become atrophic and often have

entirely disappeared The sweat glands tend to be preserved but because of the atrophy of the dermis they seem to be much closer to the epidermis than in normal skin The subcutaneous fat also becomes atrophic.

The etiology of this disease is unknown and attempts to explain its course on a systemic basis have not been convincing

Disturbances of Pigment Distribution

In normal skin five pigments are known to be present melanin melanoid carotene and reduced hemoglobin and oxyhemoglobin the normal skin color is due to a balanced mixture of these Most pathologic disturbances in skin color are due to an increase or a decrease in the amount of melanin or to the deposition of extraneous pigments or of heavy metals in the skin For example in vitiligo there is an absence of melanin pigment in the basal layer of the epidermis in the affected areas whereas in Addison's disease the amount of melanin is increased in the basal layer is scattered diffusely throughout the epidermal cells and is found in chromatophores in the cutis The pigmentation of the skin in hemochromatosis is an example of the deposition of extraneous pigments hemosiderin and hemofuscin

Argyria – In argyria the skin is bluish gray or slate colored and this pigmentation is caused by the prolonged ingestion or the repeated local application to the mucous membranes of silver salts Argyria is an example of a pigmentation caused by the deposition of a heavy metal in the skin

On microscopic examination of sections taken from a case of argyria, and stained lightly with hematoxylin and eosin or with methylene blue fine black granules of silver are found scattered throughout the dermis They do not occur in the epidermis They are especially abundant in the membranae propriae of the sweat glands (Fig 25) and in the upper part of the dermis. They are also often concentrated in the connective sheaths of hair follicles and sebaceous glands. Hill has shown that silver tends to be deposited on the elastic fibers

The silver particles can be seen in stained sections by means of the ordinary light microscope *and are not doubly refractile* They can be much more vividly demonstrated by viewing the slide under the dark field microscope. The granules of silver appear as brilliantly refractile white particles against a dark background As a differential criterion neither melanin nor hemosiderin is refractile under the dark field microscope

Lentigo.—Lentigines are small deeply pigmented smooth spots which may occur anywhere on the body They resemble freckles but they have usually been present since early childhood are darker in color and do not fade when the individual is protected from the sun

Histologically in lentigo the rete ridges of the epidermis are somewhat elongated but their tips are widened and blunted so that they are sometimes described as club shaped (Fig 26) Melanin pigment is increased in amount in the cells of the basal layer, and clear cells or melanoblasts are more numerous than in normal skin. The clear cells are found in greatest numbers at the tips of the elongated rete ridges and reveal no prominent nuclear atypia. The junction be

tween dermis and epidermis is clear cut and intact. In the upper part of the dermis chromatophores may be numerous, but there is no inflammatory reaction.

The microscopic picture of lentigo has some features in common with a junction type nevus such as the increase in melanin in the basal cells and the conspicuous clear cells However the clear cells are not found in definite nests or "theques" as they are in the nevus. The two lesions are probably closely related and transi



Fig 25 —Argyria. Fine black granules of silver present in the membrana propria of a sweat gland. (×1440) (W U neg 52-4329)



Fig. 26 —Lentigo. Club-shaped rete ridges show an increase in the number of "clear cells" or melanoblasts in the basal layer (×400) (W U neg. 52-4500)

tional pictures may be encountered. Microscopically the freckle or ephelis may be readily differentiated from lentigo. In the freckle there is an increase in melanin in the basal layer but the rete ridges are not lengthened and there is no increase in the number of clear cells.

With age, smooth brown irregular areas measuring from a few millimeters to a centimeter or more in diameter appear on the dorsa of the hands, forearms and face. Such lesions occur in approximately 25 to 30 per cent of persons who are more than 50 years of age. They are asymptomatic and bear no relationship to the general health of the individual. Cawley has studied these lesions in microscopic sections and has found that morphologically they are identical with lentigines. Their size, localized distribution and age of onset distinguished them from ordinary lentigines. They do not become malignant.

Diseases Involving Changes in Collagen or Elastic Tissue

There are a number of diseases in which the collagen of the dermis is altered. In acrodermatitis chronica atrophicans, which was discussed under Atrophies, the collagen of the dermis undergoes marked atrophy. In some of the diseases which can be classified as inflammatory lesions, such as granuloma annulare, there is focal degeneration of collagen. However, scleroderma is an example of a disease in which alterations in the collagen are the primary morphologic changes which characterize the disorder. Finally, in certain diseases such as pseudoxanthoma elasticum and Ehlers-Danlos syndrome the basic defect was originally ascribed to degeneration of elastic tissue; evidence is now accumulating to suggest that the defect may instead reside wholly or in part in the collagen.

Scleroderma.—Scleroderma may occur as localized lesions (morphea) or as a generalized disease often associated with vasomotor disturbances.

In localized scleroderma the skin in one or more discrete areas becomes smooth, firm and white. A violaceous peripheral zone surrounds these areas. Subjective symptoms are few but the disease may last for years. The localized form of scleroderma seems to be limited to the skin and rarely if ever becomes disseminated with evidence of systemic involvement.

In the generalized form of scleroderma the skin over large areas of the body becomes at first edematous or infiltrated and then stiff, ivory colored, atrophic, and bound down to the underlying tissues so that movement of the affected part may become difficult. The hands and the face are sometimes the most severely involved (acrosclerosis) and the changes of scleroderma are often associated with Raynaud's phenomena. Calcareous deposits in the affected skin are not uncommon. In addition to the skin change in generalized scleroderma systemic changes may occur. Both the striated and smooth muscle may be involved, so that muscular weakness and difficulty in swallowing and respiration occur. Weiss pointed out that the cardiac muscle can also be affected, which may lead to cardiac insufficiency.

The microscopic picture in localized and generalized scleroderma is essentially the same. In the early stages the collagen of the dermis shows edema and an inflammatory cellular infiltrate made up largely of lymphocytes may be present.

It may be scattered diffusely through the dermis but is usually dense about blood vessels. The collagen bundles are at first hypertrophied and the walls of the blood vessels are edematous.

Later in the course of the disease the epidermis becomes atrophic and the rete ridges are usually attenuated and may be obliterated (Fig 27) There may be an increase in melanin pigment. The collagen undergoes sclerosis and homogenization and fibroblasts are few in number The skin appendages become atrophic and may entirely disappear The sweat glands are usually preserved longer than the hair follicles and sebaceous glands. Lever points out that they lie "inside" the sclerotic dermis instead of at the cutaneous subcutaneous border as they do normally He believes this indicates that the thickening of the dermis is brought about not only by hypertrophy of the pre-existing collagen bundles but also by new formation of collagen at the lower border of the dermis. The connective tissue trabeculae of the subcutaneous fat are also thickened. There is usually almost no inflammatory infiltrate present Obliterative changes occur in the walls of the blood vessels

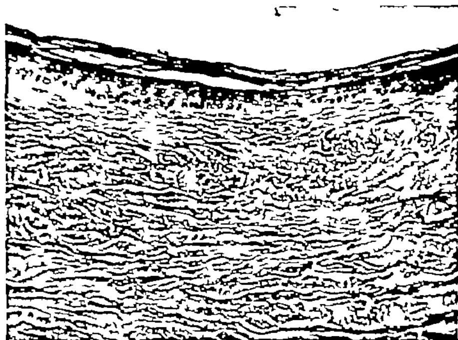


Fig 27.—Scleroderma. The epidermis is atrophic and skin appendages have disappeared. Collagen shows sclerosis and homogenization. (×170.) (W U neg 52-4323)

In fatal cases of generalized scleroderma Weiss found in the heart that the myocardial muscle fibers were isolated by newly formed connective tissue and underwent degeneration. The pleura was thickened, and in the lungs the alveolar walls were also increased in size because of the proliferation of coarse collagenous connective tissue. The esophagus and intestine may show similar changes. Thus, scleroderma is a systemic disease, but the skin lesions are so prominent that it must be considered in any discussion of cutaneous diseases.

Pseudoxanthoma Elasticum.—Clinically in pseudoxanthoma elasticum yellow to orange soft papules or plaques are found most commonly on the neck, in the

axillae in the cubital and inguinal regions and about the umbilicus (Fig 28) The involvement is often symmetrical Because of the color of the lesions the name pseudoxanthoma was given to the disorder but it is not related to xanthoma This is a hereditary disease occurring more frequently in the female Although elastic



Fig 28 —Pseudoxanthoma elasticum. Nodules about the umbilicus many of which contain an unusual amount of calcium. (W U neg 51 2732)

Fig 29 —Pseudoxanthoma elasticum. Verhoeff stain for elastic tissue In the mid dermis fibers resembling elastic fibers are fragmented, clumped and curled. (×120) (W U neg 52-4327)

tissue degeneration has been considered to be the basic defect evidence is mounting to support the concept that it is actually the collagen which is at fault (McKusick) The disease process is not limited to the skin but often includes the eye with the formation of angioid streaking of the fundus and possible dimming

of vision The cardiovascular system may be involved and result in arterial degeneration manifest clinically by coronary and/or peripheral arterial insufficiency and premature peripheral arterial calcification. In addition hypertension and hemorrhages, most commonly gastrointestinal in origin may be encountered

In sections of the skin, changes occur in the middle and lower dermis with fragmentation clumping swelling splitting, and curling of fibers having staining characteristics of elastic tissue (Fig 29) McKusick notes however that by electron microscopy and x ray diffraction these fragmented fibers have the same periodicity (640 Å) as collagen and suggests that they may represent dystrophic collagen which has assumed tinctorial characteristics similar to elastic tissue. In any event, in hematoxylin-eosin stain, the degenerated fibers are basophilic, and the diagnosis can often be suspected from a routine section. Finnerud has shown that the affected elastic fibers are rich in calcium. In the case shown in Fig 28 the nodules in the lesion, which are evident grossly were made up of calcium, but this is a somewhat unusual picture.

Cutis Hyperelastica (Ehlers-Danlos Syndrome)—Ehlers Danlos syndrome denotes a hereditary disorder of connective tissue manifested by the clinical features of hyperelasticity of the skin hyperextensibility of joints skin fragility with pseudotumor formation, and fragility of blood vessels There is great distensibility and elasticity of the skin which can often be pulled out for several inches, but when it is released it assumes its normal contour and does not hang in folds The skin is fragile so that areas of trauma, especially the elbows and knees are often covered with scars of a unique parchment thin shiny hyperpigmented type ("papyraceous" scar) Semitranslucent pseudotumors or subcutaneous nodules are often present at sites of trauma and may be fibrous often associated with a foreign body reaction or calcific. Ease of bruising is often noted Skeletal ocular and certain visceral manifestations may also be encountered

The "India rubber men" of the circus are examples of this syndrome and utilize the marked stretching of skin and joint mobility in their contortions. One point of particular interest to the surgeon is the skin friability Suture of lacerations or operative sites may be difficult due to the suture cutting through the friable skin

The nature of the defect in this disorder is not clear An increase of elastic tissue has been proposed as its morphologic expression however the elastic tissue encountered in skin biopsies has been reported to be normal or even decreased in some cases

A change in the molecular structure of individual collagen fibers or in the pattern of organization of these fibers into collagen bundles has been suggested. Jansen has described a disorderly arrangement of poorly united collagen bundles in Ehlers Danlos syndrome in contrast to the well united collagen bundles seen normally

Inflammatory Diseases of Unknown Etiology

Although the inflammatory diseases of the skin are very numerous the cause of many of them is unknown. Nevertheless a large number of them have a specific histopathologic picture and a biopsy can be helpful in establishing the

diagnosis The position of the cellular infiltrate and the types of cells of which it is composed, as well as the presence or absence of vesicles, are important factors in identifying specific lesions

Psoriasis.—Psoriasis is one of the most common skin disorders. It is a chronic disease and is characterized by multiple reddish brown papules or plaques which are found most often on the extensor surfaces of the extremities and on the chest (Fig 30) Lesions may occur, however, on any part of the body The lesions are dry, clearly defined, and covered with imbricated silvery scales When the scales are removed, fine bleeding points are revealed If the lesions are numerous, they are usually in different stages of development and may vary in size.

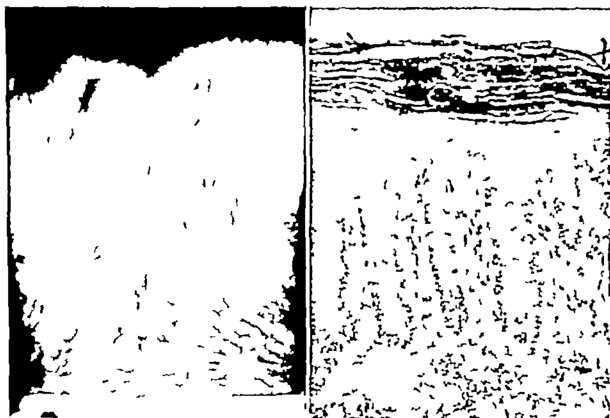


Fig 30.—Psoriasis. (W U neg 5? 5562.) (Courtesy Dr James Sisk, St. Louis Mo)

Fig 31.—Psoriasis. The epidermis shows parakeratosis absence of the granular layer and regular acanthosis with lengthening of the rete ridges. A Monro abscess is present in the stratum corneum. The dermis is edematous and a moderately dense perivascular inflammatory cellular infiltrate is present. (×135) (W U neg 52-4326.)

The histopathologic picture is distinctive (Fig 31) The epidermis shows *pronounced parakeratosis and the granular layer is absent.* There is regular acanthosis with lengthening of the rete ridges which are often rounded at their tips and resemble test tubes Sometimes adjacent rete ridges are fused Numerous mitotic figures are often found in the epidermis The layers of the epidermal cells over the dermal papillae (suprapapillary plates) are reduced in number There may be some intracellular edema in the epidermis but intercellular edema is almost never found

The papillary portion of the dermis is usually edematous, and the capillaries in the dermal papillae are conspicuous because they are dilated and tortuous. In the upper dermis a moderately dense cellular infiltrate is present which tends to be perivascular in arrangement. It is made up largely of lymphocytes and histiocytes. A few leukocytes are found in the epidermis. They apparently penetrate through the epidermis and collect in small masses in the parakeratotic stratum corneum. These collections are called Monro microabscesses, but they are not entirely pathognomonic of psoriasis

The bleeding points which appear when the scale is removed from a lesion of psoriasis are explained by the thinness of the suprapapillary plates and the dilation of the capillaries in the dermal papillae which are readily exposed by slight trauma.

Lichen Planus.—Lichen planus is primarily a chronic or subacute disease of the skin, but lesions may also occur on the mucous membranes. The lesions are multiple and are usually limited in distribution but they may occasionally be generalized. They are very pruritic. The typical lesion is a small, shiny violaceous polygonal papule which may be umbilicated. Coalescent papules may be covered by fine adherent silvery scales. Occasionally vesicles occur on the top of each papule (bullous lichen planus) Old lesions especially those on the lower extremities sometimes form thickened elevated brown to purple patches which are verrucous on the surface. Such lesions are called hypertrophic lichen planus. When the disease occurs on the oral mucosa it must be differentiated from leukoplakia. Occasionally oral mucosal lesions may be present for many months prior to the development of cutaneous lesions

The microscopic picture of lichen planus is usually quite diagnostic (Fig 32) The epidermis shows hyperkeratosis without any areas of parakeratosis. The granular layer is thickened and there is acanthosis The rete ridges are lengthened but not to as great an extent as they are in psoriasis. The tips of the rete ridges are usually pointed, so that the epidermis has what Lever aptly describes as a saw tooth appearance. In early lesions the basal layer may show liquefaction or hydropic degeneration. Immediately beneath the epidermis in the upper part of the dermis a dense cellular infiltrate, made up largely of lymphocytes and histiocytes is present. The infiltrate is clearly limited to the papillary portion of the dermis, and the lower border is usually sharply defined The cells of the infiltrate penetrate between the cells of the basal layer of the epidermis which makes the epidermodermal junction rather indistinct There are no changes in the blood vessels. In involuting lesions the epidermis may become quite atrophic, but the cellular infiltrate in the upper third of the dermis persists, although it may be decreased in density Chromatophores filled with melanin may be conspicuous in the dermis.

The lesions on the mucous membranes are similar morphologically to the cutaneous lesions, but both microscopically and clinically these lesions are sometimes difficult to distinguish from leukoplakia.

In bullous lichen planus the vesicles form at the junction of the dermis and the epidermis. In hypertrophic lichen planus the epidermis is distinctly thickened and there is pronounced hyperkeratosis with plugging of the hair follicles.

The cellular infiltrate in the dermis is not so sharply limited to the upper part of the dermis but may be found also about blood vessels deeper in the dermis

Some skin eruptions caused by drugs such as Atabrine and bismuth produce a microscopic picture which is indistinguishable from lichen planus



Fig 32 – Lichen planus The epidermis shows hyperkeratosis thickening of the granular layer and acanthosis with irregular lengthening of the rete ridges so that they have a "saw tooth" appearance Immediately below the epidermis in the upper part of the dermis, a bandlike zone of cellular infiltrate made up of lymphocytes is present. (×100) (W U neg 52-4404)

Lupus Erythematosus. –The clinical classifications of the various phases of lupus erythematosus have been many but the one suggested by O'Leary and given in detail by Kierland is comprehensive. This classification divides the disease into four types (1) a chronic localized discoid type which is most common and is limited to the face (2) a generalized discoid or chronic disseminated type which is discoid lupus erythematosus in which lesions occur elsewhere than on the face, (3) a subacute disseminated type and (4) an acute disseminated type. In the first two types the symptoms of the disease are essentially limited to the skin while in the last two the disease is systemic. Correlation of the microscopic picture with the clinical type of the disease is not always possible as shown by the studies of Montgomery

In the first type chronic localized discoid lupus erythematosus the lesions are erythematous clearly delimited, and oval or round in shape. They are located most commonly on the "butterfly area" of the face, but the ears and scalp may be involved (Fig 33) The lesions progress peripherally and the border is slightly raised and infiltrated. The involved areas may be covered by adherent scales and on close inspection the hair follicles will be seen to be dilated and plugged with keratin. In old lesions the center may become slightly depressed and atrophic, and upon involution of a lesion a smooth atrophic scar remains. This type of the disease progresses slowly and may be present for years without affecting the general health of the patient.

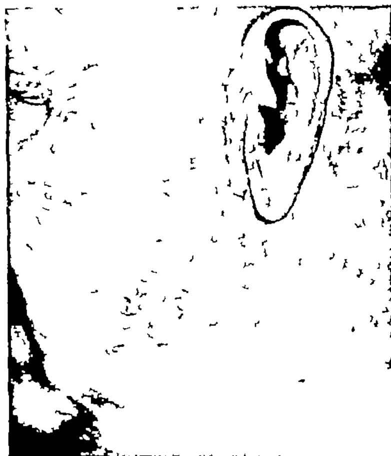


Fig. 33 —Chronic, localized discoid lupus erythematosus. (W U neg 52 5560) (Courtesy Dr James Sisk, St. Louis, Mo.)

The second type, generalized discoid or chronic disseminated lupus erythematosus presents the same kind of lesions as does the first type, chronic localized discoid, but they are more widely distributed and are not limited to the face.

In subacute disseminated lupus erythematosus the cutaneous lesions develop on the face and on other portions of the body, especially the thorax, the arms and legs. They consist of erythematous, irregularly shaped patches that tend to coalesce. Systemic symptoms such as leukopenia, anemia, reversal of the albumin globulin ratio fever, and malaise occur Remissions take place, and transition into the fatal acute form is not very common. The subacute form is not often

seen It may appear in patients who have or have not had the discoid type of the disease Montgomery in a study of [illegible] cases of subacute lupus erythematosus found that 17 per cent had previously had the discoid type of disease

In the acute disseminated type of lupus erythematosus the systemic symptoms are severe and death usually occurs within a year or less The cutaneous lesions are less well defined than in the other types and may even be absent The skin lesions often appear first on the face as a diffuse edematous erythema which may spread to other portions of the body They may be only transitory The



Fig 34 —Discoid lupus erythematosus The epidermis shows moderate hyperkeratosis with plugging of one hair follicle atrophy and liquefaction degeneration of the basal layer The dermis shows edema and a perivascular and perifollicular cellular infiltrate is present. (×145) (W U neg 52 4405)

systemic symptoms may include leukopenia and anemia, fever arthralgia or arthritis, evidence of renal irritation or nephritis cardiac symptoms, and a reversal of the albumin-globulin ratio Associated nonbacterial verrucous endocarditis, the Libman-Sacks syndrome occurs in some cases of acute disseminated lupus.

The same histopathologic changes are present in the cutaneous lesions of all types of lupus erythematosus In the discoid forms of the disease the picture is usually more clearly defined (Fig 34) The epidermis shows hyperkeratosis and the hair follicles are distended and plugged with keratin. There are areas of

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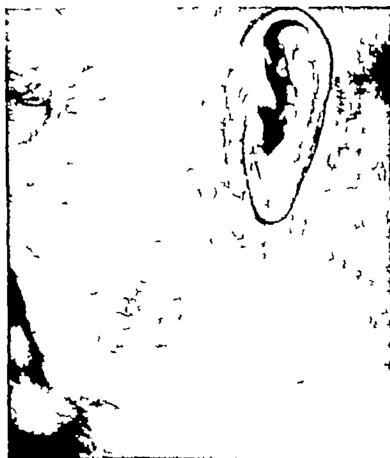


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acanthosis alternating with areas of atrophy Liquefaction degeneration in the basal layer is often conspicuous. These changes in the epidermis are thought to be secondary to the inflammatory changes in the dermis and may not be present in an early lesion The dermis shows pronounced edema with dilatation of blood vessels and lymph spaces A perivascular cellular infiltrate, which is made up largely of *lymphocytes, is present and is usually more densely distributed about* the skin appendages. Chromatophores containing melanin pigment are frequently numerous in the upper part of the dermis. No changes occur in the walls of the blood vessels The basophilic degeneration of the collagen and elastic tissue of the upper part of the dermis which has sometimes been given as one of the characteristic histologic findings in discoid lupus erythematosus is probably only an age change. The disease occurs on exposed parts of the body and such changes would be expected in patients who are middle aged or older



Fig 35 —The "L.E." cell characterized by a homogeneous mass of altered nucleoprotein engulfed by a polymorphonuclear leukocyte. (W U neg 50-1658)

After a study of 102 specimens of cutaneous lesions of disseminated lupus erythematosus and 17 typical skin specimens of discoid lupus erythematosus, McCreight concluded that the same histologic changes occur in all the various clinical types of the disease and that distinction of the type based on histologic grounds alone is impossible. Liquefaction of the basal layer, edema of the dermis, and dilatation of the superficial capillaries and lymph spaces are sometimes more marked in disseminated types of the disease, but the cellular infiltrate is decreased in amount. These changes may be dependent however on the age of the individual lesion rather than on the type of the disease. Klemperer reported hyalinization and fibrinoid degeneration of the connective tissue of the dermis, but McCreight was not able to confirm these findings in his material since he found these changes relatively infrequently either in the connective tissue or in the blood vessel walls.

The visceral lesions in acute disseminated lupus erythematosus are discussed at length in a paper published in 1941 by Klemperer

In cases of disseminated lupus erythematosus, a useful diagnostic tool, first reported by Hargraves in 1948 has been the so-called L.E." cell (Fig 35) It was discovered in the bone marrow of patients with the acute disseminated type of the disease and is a polymorphonuclear leukocyte which contains in its cytoplasm a round, homogeneous basophilic or smoky mass of altered nucleoprotein.

In addition to the bone marrow this cell has been found in the circulating blood in clotted blood and in blister fluid of patients These "L E" cells are found in largest numbers during the severe stages of the disease and with difficulty during remissions The formation of L.E cells seems to depend upon a combination of leukocytic nuclear debris viable phagocytic leukocytes, and a so-called plasma factor found in patients with systemic lupus erythematosus The demonstration of L.E cells is a valuable aid in the diagnosis of acute disseminated lupus erythematosus

Dermatomyositis —The clinical picture of dermatomyositis resembles that of disseminated lupus erythematosus to such a degree that differentiation is sometimes difficult In dermatomyositis both skin and skeletal muscle are involved The skin lesions vary in appearance but they most often occur on the face chest and arms They are frequently rather well-defined areas of erythema and edema Any of the skeletal muscles may be involved and the clinical signs are weakness *muscular tenderness and pain and later atrophy which may result in contractures* The course of the disease may be acute with severe and rapidly progressive symptoms or it may be chronic. The disease is fatal in a large percentage of cases

The microscopic picture in the cutaneous lesions is nonspecific and the diagnosis cannot be made on the skin specimens alone The dermis is usually edematous and a moderate perivascular cellular infiltrate made up largely of lymphocytes may be present

If a specimen is taken from a striated muscle that is clinically affected, microscopic changes are apparent The muscle bundles show variability in diameter and granular fibrinous or vascular degeneration There is loss of transverse striations and occasionally coagulation or hyalinization of the sarcoplasm Collections of lymphocytes histiocytes plasma cells and fibroblasts are found either about blood vessels or invading the muscle diffusely Muscle nuclei are often increased in number which may indicate an attempt at muscle repair

There appears to be an increased association of malignancy with dermatomyositis. Schuermann reviewed 336 published cases of dermatomyositis and found 31 associated malignant neoplasms This was found statistically to be five times greater than would have been expected in the general population Dowling reported additional cases and noted that in all instances the malignancy apparently preceded the onset of dermatomyositis and that in four cases there was symptomatic improvement of the dermatomyositis when the neoplasm was treated (operation or radiotherapy)

Dermatomyositis lupus erythematosus and scleroderma have certain characteristics in common but if the skin lesions alone are considered the first is nonspecific and the last two have distinct histopathologic pictures

Urticaria Pigmentosa.—The characteristic lesion of urticaria pigmentosa is a pigmented macule or nodule, about which an urticarial wheal will develop when the lesion is irritated The lesions are multiple and often cover most of the body surface. They usually appear during the first year of life and the general health of the patient is not affected but in some instances the disease has occurred in adult life (Berlin) It runs a chronic course, and after a period of years new lesions

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no longer appear but the areas of hyperpigmentation may be permanent Al though the disease is relatively rare, it should be mentioned because the lesions are occasionally clinically confused with xanthoma or other pigmented tumors The microscopic picture is very characteristic.

The most distinctive finding microscopically is the presence in the upper part of the dermis of a perivascular infiltrate made up of mast cells (Figs 36 and 37)



Fig 36.—Urticaria pigmentosa. In the dermis is a perivascular cellular infiltrate made up almost entirely of mast cells. (×200) (W U neg 52-4328)

Fig 37.—Mast cells in the infiltrate stained with Unna's polychrome methylene blue to show the metachromatic granules in the cytoplasm. (×1450) (W U neg 52-4400)

When nodules are present, the entire lesion is composed of closely packed mast cells. In sections stained routinely mast cells may not be recognized. When one of the metachromatic dyes is used, such as toluidine blue or Unna's polychrome methylene blue after formalin or alcohol fixation, the metachromatic granules in the cytoplasm of the mast cells are readily demonstrated (Figs. 36 and 37) If the lesion has been irritated prior to doing the biopsy the dermis will show edema. Melanin is increased in the cells of the basal layer of the epidermis, and sometimes chromatophores are numerous in the dermis. Histologically these lesions may be mistakenly interpreted to be intradermal nevi

Ellis has reported a case of urticaria pigmentosa with autopsy findings in a 1 year-old Negro girl who died of other causes In this baby with urticaria pigmentosa the number of mast cells found in the different organs were compared with those in similar tissues taken from normal infants of the same age who died of traumatic lesions A pronounced increase in mast cells was found in the liver spleen thymus bone marrow pancreas and lymph nodes, and a less striking increase in the lung and kidney Other reported autopsied cases have subsequently substantiated the fact that urticaria pigmentosa is, indeed, a systemic disease whose most readily recognizable clinical manifestation is cutaneous



Fig 38 —Granuloma annulare In the upper part of the dermis are two areas of collagen necrosis surrounded by a radially arranged cellular infiltrate made up of lymphocytes histiocytes, and fibroblasts. (×100) (W U neg 52 4324)

Granuloma Annulare.—The lesions of granuloma annulare are small firm, white or red nodules which are usually grouped in a ring The border is frequently raised and the center may be normal or atrophic. The lesions vary greatly in number and are found most commonly on the hands and feet The patients are often children. The disease has been thought by many to have a tuberculous etiology but the evidence is not convincing

In a typical well-developed lesion (Fig 38) areas of fibrinoid necrosis which are surrounded by a cellular infiltrate made up of lymphocytes, histiocytes and

fibroblasts are found in the dermis The cells of the infiltrate have a radial arrangement and often show a tendency to be arranged in palisade like formation about the area of necrosis. A few foreign body giant cells may also be present among the cells of the infiltrate. A mucin stain will usually show mucin in the area of necrosis and in the surrounding connective tissue and is often useful in histologically differentiating this lesion from necrobiosis lipoidica diabeticorum which is mucin negative. The blood vessels show no pathologic changes

In early lesions the areas of necrosis may be absent. The collagen bundles, however, instead of being parallel to the surface of the skin as they are normally have a disorderly arrangement. Infiltrating between them are often single rows of lymphocytes and histiocytes. Some of the collagen bundles in such areas show evidence of degeneration. Although these areas are poorly defined, they sometimes have a starlike shape, with the rows of histiocytes and lymphocytes radiating out from the center

Lever calls the areas which show necrosis, foci of complete collagen degeneration and those where necrosis is absent, foci of incomplete collagen degeneration. Both types may occur together or separately

A picture very similar to that of granuloma annulare is found in the rheumatic or rheumatoid nodule Small firm subcutaneous nodules may develop in patients with rheumatic fever or rheumatoid arthritis These lesions too consist of a central area of necrosis a mid zone of histiocytes and fibroblasts, frequently arranged radially and a peripheral zone of edema slight fibrosis, and cellular infiltration. The chief difference microscopically between the rheumatoid nodule and the typical lesion of granuloma annulare is that the first is found in the subcutaneous tissue and the second in the dermis.

Chondrodermatitis Nodularis Chronica Helicis.—The lesions known as chondrodermatitis nodularis chronica helicis are small round, firm nodules that usually occur on the border of the helix of the ear The surface may be flat or may have a slight depression in the center filled with an adherent scale. The nodules are usually firmly attached to the underlying cartilage and are painful upon pressure. The lesions occur predominantly in men and are occasionally bilateral. They are sometimes clinically and/or pathologically mistaken for carcinoma or a keratosis. Complete excision of the lesion including the involved area of cartilage, provides excellent therapeutic results. If, however a portion of degenerated cartilage is retained, pain usually persists and the lesion will often recur

The histologic picture is distinctive. The epidermis shows hyperkeratosis and pronounced acanthosis The dermis reveals focal fibrinoid degeneration, proliferating granulation tissue, and a variable chronic inflammatory cell infiltrate. Finally the cartilage exhibits evidence of perichondritis usually with cartilage degeneration. The pathogenesis of this process is not clearly understood.

Inflammatory Nodular Lesions of the Legs

On first thought inflammatory nodules of the legs would seem not to warrant separate consideration. However biopsies are frequently done on such lesions since they often present clinical problems in diagnosis and often cause considerable

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the legs especially on the thighs and on the trunk As new lesions occur patients usually have recurrence of malaise and fever An afebrile variant of this disease has been described. When the cutaneous lesions heal a depressed scar results. The etiology of the disease is unknown. Internal adipose tissue as well as the subcutaneous fat may be involved as has been shown at the time of autopsy

In this disease the dermis shows only a slight perivascular lymphocytic infiltration. In the subcutis however, histiocytes filled with lipoid material almost replace the fat cells, and some lymphocytes and plasma cells may be present. The connective tissue septae between the fat lobules are not prominently thickened. Occasionally some foreign body giant cells are found Changes in the blood vessels are minimal. Eventually some of the lipophages become necrotic and are replaced by fibrous tissue.

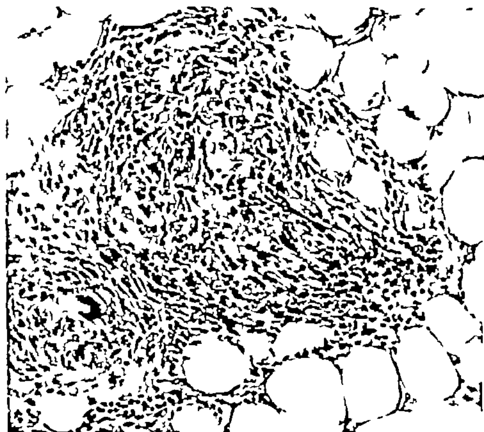


Fig 39.—Erythema induratum. A nodule in the subcutaneous fat made up of epithelioid cells giant cells and lymphocytes in tubercle like arrangement. (×300) (W U neg 52-4331)

Inflammatory Diseases Resulting in Vesicle Formation

Eczema.—Ormsby defines eczema as an acute subacute or chronic inflammation of the skin characterized by erythema or by the appearance of isolated or grouped papules, vesicles or pustules occurring in uniform, multiform or modified types upon a reddened infiltrated base, accompanied by itching or burning sensations and resulting in weeping and crusting in infiltration and scaling caused by varied and complex internal and local factors." Although the clinical types of

eczema are legion histologically they all can be placed into a group which has rather definite characteristics From the standpoint of the surgical pathologist it is usually not important to attempt to diagnose the clinical varieties of eczema However to be able to put a given specimen into this group of diseases is sometimes helpful For example in specimens taken from the nipple of the breast a differential diagnosis between Paget s disease and eczema may have to be made and lesions that are thought clinically to be lupus erythematosus may be an eczema on microscopic examination

Microscopically in eczematous dermatitis the most striking changes are in the epidermis Parakeratosis and acanthosis are characteristic Intercellular edema in the epidermis has usually progressed to the point of spongiosis and there are intraepidermal vesicles formed by coalescence of the spaces between cells in the areas of spongiosis and by liquefaction degeneration of individual cells The dermis is also edematous and blood vessels and lymph spaces are dilated A moderate perivascular cellular infiltrate is present which is made up largely of lymphocytes together with a few eosinophils histiocytes and polymorphonuclear leukocytes Leukocytes penetrate into the epidermis and sometimes the surface of the skin is covered by a crust made up of extravasated fluid and leukocytes

Dermatitis Herpetiformis.—Clinically dermatitis herpetiformis is a chronic recurrent skin disease characterized by groups of vesicles papules or pustules which are symmetrically distributed The lesions are usually very pruritic The eruption may vary in extent from a few patches to a generalized distribution The parts of the body most frequently affected are the extensor surfaces of the extremities the sacral region and the scapular regions The general health is unaffected

The vesicles of dermatitis herpetiformis are "pressure vesicles and are usually located at the junction of the dermis and the epidermis (Fig 11) They may occur within the epidermis however They are thought to be formed by the pressure of a rather sudden inrush of fluid into that part of the skin. They are filled with serum fibrin and large numbers of eosinophils as well as with some polymorphonuclear leukocytes and lymphocytes. The dermis is edematous, and the blood vessels and lymph spaces are dilated A rather dense cellular infiltrate is present in the upper part of the dermis and eosinophils are usually present in large numbers The inflammatory cellular infiltrate is usually more dense than that in bullous pemphigoid However there are cases in which it is difficult to determine both clinically and microscopically whether the lesions are those of dermatitis herpetiformis or of bullous pemphigoid Bullous erythema multiforme may also be difficult to differentiate from dermatitis herpetiformis. At times it is necessary to obtain clinical information to supplement the histologic findings in order to arrive at a competent diagnosis

Pemphigoid (Bullous Pemphigoid) —This term denotes a frequently extensive cutaneous eruption of usually tense bullae which may rupture to produce denuded areas. These areas differ from true pemphigus in the absence of progressive peripheral enlargement of the denuded area and in the tendency to healing Other dissimilarities include the findings that this disease may occur in childhood, has few or no mucous membrane lesions usually has a chronic benign

course does not ordinarily markedly impair the health of the patient, and rarely results in death except in aged persons. In spite of these clinical differences pemphigoid has been considered to be a benign type of pemphigus vulgaris by many observers others have suggested that it was more closely related to dermatitis herpetiformis. Since clinically it does not conform entirely to either true pemphigus or dermatitis herpetiformis and is histologically distinct from pemphigus Lever has suggested the term bullous pemphigoid to categorize this cutaneous disease.

Microscopically, pemphigoid presents as a subepidermal bulla without evidence of acantholysis. The absence of acantholysis rules out a histologic diagnosis of pemphigus. A slight to moderate inflammatory infiltrate including lymphocytes polymorphonuclear leukocytes, and variable numbers of eosinophils is present in the underlying dermis. From a purely histologic standpoint, great difficulty may be encountered in distinguishing this lesion from those of bullous erythema multiforme or dermatitis herpetiformis.

Pemphigus.—Pemphigus is a severe frequently lethal vesicular eruption in which bullae form either continuously or in successive crops. The disease was formerly so often fatal that if a patient survived the accuracy of the diagnosis was questioned. Since the advent of corticosteroid therapy however the prognosis has been greatly improved The etiology of the disease is unknown.

At least four morphologic types of pemphigus are usually described and designated as pemphigus vulgaris pemphigus vegetans pemphigus foliaceus, and pemphigus erythematodes (Senear Usher type) Pemphigus vulgaris is characterized by fluid filled bullae which arise on skin that appears to be normal. They may rupture, leaving an eroded surface, or they may involute without rupturing In pemphigus vegetans the initial bullae soon become eroded and covered by a vegetating papillomatous mass. Pemphigus foliaceus is a relatively rare form of the disease. The lesions are at first flaccid bullae which rapidly rupture and become covered with yellowish-brown crusts. The whole body usually becomes involved so that the entire skin appears to be exfoliating A similar if not identical disease called Fogo salvagem has been described it is endemic in Brazil and is histologically similar if not identical, to pemphigus foliaceus but differs in its familial tendency and associated apparent endocrine disturbances (Vieira) Pemphigus erythematodes is a relatively mild form of chronic pemphigus. The bullae are soon transformed into crusted erythematous areas which resemble the lesions of lupus erythematosus.

Histologically the characteristic lesion of pemphigus is an acantholytic vesicle located intraepidermally (Fig 40) The lesion develops by focal degeneration of epidermal cells with disappearance of the intercellular bridges loss of cohesiveness, and resultant cleft and bulla formation. These degenerating epidermal cells or groups of cells slough irregularly into the cavity (Tzanck cells) thereby producing a rather ragged margin about the bulla The acantholytic cleavage may extend down around dermal appendages. The presence of the degenerating cells forms the basis for various cytodiagnostic tests including smears made from scrapings of vesicle bases (Tzanck test) from bulla fluid, and from biopsy touch preparations. Biopsy however continues to be the most reliable diagnostic method.

In this, as with all bullous lesions, small intact bullae should be selected and totally excised if adequate histopathologic interpretation is to be obtained.

In pemphigus vulgaris the bullae are predominantly suprabasilar in location. Only a mild inflammatory infiltrate composed of lymphocytes, polymorphonuclear leukocytes and eosinophils is present within the dermis underlying the bulla. In later lesions the epidermis may show verrucous hypertrophy with acanthosis and papillomatosis.

Pemphigus vegetans is usually considered to be a verrucous phase of pemphigus vulgaris. Its histologic picture is unique. Acanthosis, papillomatosis and microabscesses are present. The abscesses are composed of eosinophils and a few acantholytic epidermal cells. The underlying dermis reveals a diffuse cellular infiltrate in which eosinophils are very numerous. The epidermal hyperplasia and the microabscesses may suggest bromoderma or one of the deep fungus infections, but the very conspicuous eosinophils are absent in these diseases.

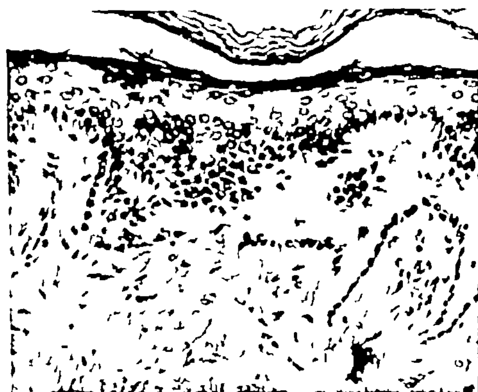


Fig. 40. Pemphigus. Intraepidermal bulla produced by acantholysis at the suprabasal level. The floor of the bulla is made up largely of basal cells; the cavity contains free squamous cells, a few inflammatory cells and fibrin; the roof is made up of epidermal cells. There is little inflammatory reaction in the dermis. (× 240.) (W.U. neg. 52-7101.)

Early lesions of pemphigus foliaceus show bullae usually located in the upper portion of the spinous layer. There may be loss of the vesicle roof and the microscopic picture resembles that of a generalized exfoliative dermatitis; however, careful evaluation will still reveal acantholytic changes in the superficial area. Later hyperkeratosis, parakeratosis and acanthosis develop. The dermis contains a moderate chronic inflammatory cell infiltrate which includes eosinophils.

In pemphigus erythematodes bullae are not so numerous or prominent as in pemphigus vulgaris. The epidermis usually shows areas of hyperkeratosis with

some follicular plugging parakeratosis and moderate acanthosis. Acantholysis may or may not be well defined. Differentiation histologically from lupus erythematosus may be difficult, but the acantholysis and absence of epidermal atrophy and liquefaction degeneration of the basal layer are distinguishing points.

Diseases Caused by Bacteria

Hidradenitis Suppurativa.—Since one of the preferred treatments for an advanced case of hidradenitis suppurativa is surgical excision this disease is of importance to the surgical pathologist. As the name implies it is an infectious disease of the apocrine sweat glands. Both *staphylococci and streptococci* have



Fig 41—Hidradenitis suppurativa. Axilla. Nodules, sinuses, and cordlike bands develop as a result of a bacterial infection of the apocrine sweat glands. (W U neg 52-4478)

Fig 42—Hidradenitis suppurativa. An inflammatory infiltrate about the sweat gland which has destroyed some of the glands. (×150) (W U neg. 52 4407)

been isolated from the lesions. The first symptom is the appearance of a subcutaneous nodule in apocrine gland bearing areas, namely axillary or pubic regions, about the anus and occasionally about the breast. More nodules develop which coalesce to form cordlike elevated bands (Fig 41) Some of the nodules may break down and discharge pus. The disease spreads to the subcutaneous tissue and sinuses are formed often with epithelial bridges between them. Lesions about the anus may perforate into the rectum and anal fistulae result.

In early lesions an inflammatory cellular infiltrate is found within and around the lumina of apocrine glands. The infection spreads by way of the lymphatics,

and some sweat glands are found distended with polymorphonuclear leukocytes; others are destroyed by the inflammation (Fig. 42). In the early stages the cellular infiltrate is made up of polymorphonuclear leukocytes and later of lymphocytes and plasma cells. Foreign body giant cells may be present. The epidermis and the upper part of the dermis are involved only after extensive spread of the infection.

Tuberculosis. Tuberculosis of the skin is not a very common disease in the United States, but it occurs in many different forms, and no entirely satisfactory



Fig. 43. Lupus vulgaris. Typical tubercles in the dermis. Group of foreign body giant cells at left. (× 105.) (W.U. neg. 52-4506.)

classification of the lesions exists. From the standpoint of the pathologist, Montgomery's is perhaps the most satisfactory. He divides the lesions into two groups: localized (inoculation) tuberculosis and disseminated (hematogenous) tuberculosis. Under inoculation tuberculosis he considers (1) the primary tuberculous complex or tuberculous chancre and (2) secondary inoculation in a person who has already had tuberculosis (these patients are usually free of active tuberculosis in the viscera). Under hematogenous infections are the large group of so-called tuberculids. These lesions are thought to be caused by the hematogenous dis

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Fig 44 North American blastomycosis (W U neg 49 1329)

Fig 45 North American blastomycosis Pseudoepitheliomatous hyperplasia of the epidermis with an intraepidermal microabscess Granulomatous infiltrate in the dermus in which many giant cells containing the organism are present. (W U neg 49-6385)

Fig 46 North American blastomycosis showing two-budding form of the doubly contoured organism (W U neg 49 6391)

semination of tubercle bacilli in patients who have a high immunity to tuberculosis. The internal focus from whence the organisms come usually cannot be found. The tuberculin test is positive in patients with most types of tuberculids but demonstration of organisms in the skin lesion either in paraffin sections or by animal inoculation can rarely be accomplished.

Lupus vulgaris is an example of secondary inoculation or reinfection tuberculosis. The lesions are circumscribed reddish-brown patches which are made up of small individual nodules. These patches may coalesce to cover rather large areas. When a glass slide is held against the lesion and blood pressed out (diascopy) the nodules have a light brown color and they have been called apple jelly nodules. The lesions usually occur on the face.

Microscopically the lesions are characterized by typical tubercles in the dermis (Fig 43) They are made up of a central area of epithelioid cells among which are scattered giant cells of the Langhans type and a peripheral zone of lymphocytes. The tubercles may be conglomerate or discrete There is usually no caseation necrosis. A degenerated hair or the destruction of tissue by the disease may cause a foreign body giant cell reaction. Changes in the epidermis are secondary and may vary from atrophy to hyperplasia to ulceration. The presence of ulceration may be useful in clinically differentiating lupus vulgaris from sarcoidosis since in the latter ulceration is rarely encountered Tubercle bacilli can only be demonstrated occasionally in paraffin sections.

The hematogenous forms of tuberculosis of the skin usually present microscopically a tuberculoid reaction but the details of their morphologic structure vary Erythema induratum which was discussed previously is generally classified in the hematogenous group

Diseases Caused by Fungi

Of the fungous diseases, two that produce cutaneous lesions are important from the standpoint of diagnosis of tissue sections. North American blastomycosis is an uncommon, but not rare disease which has a rather definite clinical picture. Microscopically it must be differentiated from tuberculosis verrucosa cutis, one of the types of inoculation tuberculosis characterized by hyperplasia of the epidermis and even at times from squamous carcinoma. Chromoblastomycosis (chromomycosis) is a rare disease and clinically it is often mistaken for carcinoma.

North American Blastomycosis.—North American blastomycosis is caused by the organism *Blastomyces dermatitidis* and except for a few cases from Canada and England the disease has been reported only from the United States. *Blastomyces dermatitidis* is a spherical yeastlike organism which measures from 8 to 15 microns in diameter It has a relatively thick capsule which makes it appear to be doubly contoured on microscopic examination. It multiplies by simple budding (Fig 46) each organism producing one bud.

Two clinical forms of the disease are recognized the systemic and the cutaneous. The portal of entry for the systemic type is usually the respiratory tract, and dissemination of the disease to lungs, bone, liver spleen and other organs follows. The skin may be secondarily involved. In primary cutaneous blastomycosis the organism gains entry through the skin of exposed parts of the body and



[illegible] Forearm

Fig 48 Chromoblastomycosis. Epidermis shows hyperkeratosis and irregular acanthosis. A granulomatous infiltrate in the dermis (W U neg 49-6559)

Fig 49 Chromoblastomycosis A small cluster of organisms. One shows a cross wall. (W U neg 49-6388)

the cutaneous lesions may remain localized for a long period of time. In both types of the disease the skin lesions are verrucous plaques (Fig 44) which spread peripherally and have on the raised border many small abscesses. In the primary cutaneous type the lesions tend to heal in the center in the systemic form they may ulcerate, and subcutaneous abscesses may occur The organisms may be identified by smear and by culture of material removed from the cutaneous or subcutaneous abscesses.

In tissue sections (Fig 45) the epidermis shows pronounced acanthosis, and the epidermis grows downward into the dermis irregularly The distortion of the epidermis is so marked that the process is often described as pseudoepitheliomatous hyperplasia. Within the epidermis are microabscesses, which are small focal collections of polymorphonuclear leukocytes among which may be scattered a few Langhans giant cells. In the dermis miliary abscesses and a diffuse dense infiltrate made up of lymphocytes polymorphonuclear leukocytes histiocytes, plasma cells, and a variable number of Langhans giant cells may be present. Organisms are often found in the giant cells and scattered among the cells of the infiltrate.

Chromoblastomycosis (Chromomycosis) —Chromoblastomycosis is a rare disease in the United States but is more common in Central and South America. It is included here because in the six cases encountered in this laboratory all were thought clinically to be carcinoma and the diagnosis was made by examination of tissue sections. The disease may be caused by any one of a group of closely related organisms *Hormodendrum pedrosoi Hormodendrum compactum* or *Phialophora verrucosa* The lesions are limited to the skin and are verrucous nodules or plaques (Fig 47) They are most commonly found on the extremities or on the head and, in most instances, have followed trauma. They develop very slowly

The organisms appear in tissue as single or clustered oval, thick walled dark brown bodies which are approximately 10 microns in diameter They multiply by the formation of a cross wall in the parent cell and not by budding (Fig 49)

Tissue sections of the lesion are similar to those of North American blastomycosis (Fig 48) The epidermis shows hyperkeratosis, acanthosis pseudoepitheliomatous hyperplasia, and microabscess formation although these changes are usually less extensive than in blastomycosis In the dermis a granulomatous reaction is present. The cellular infiltrate is composed of polymorphonuclear leukocytes, lymphocytes, plasma cells histiocytes eosinophils and Langhans giant cells The organism may be found singly or in clusters among the cells of the inflammatory infiltrate or in giant cells and is readily visible because of its distinct brown color

"Insect" Bites

The bites of ticks, mosquitoes chiggers and other arthropods produce in certain persons persistent nodular or papular lesions which may or may not ulcerate. These lesions may be very difficult to diagnose both clinically and microscopically

Histologically in some cases the epidermis shows pseudoepitheliomatous hyperplasia and in others spongiosis and vesicle formation (Fig 1) Sometimes a relatively uniform acanthosis associated with hyperkeratosis and focal parakeratosis

is present. In the dermis a pronounced inflammatory reaction occurs (Fig 50) Sometimes masses of cells are found which resemble large lymphoid follicles with germinal centers. Many eosinophils, plasma cells, and histiocytes are usually present. Binucleate histiocytes with partially overlapping nuclei, which resemble



Fig 50 —Tick bite. Part of the head of the tick is present in the mid-dermis with a pronounced inflammatory reaction about it. (×100) (W U neg 52-4508)

the Reed-Sternberg cells of Hodgkin's disease may be found. Mitotic figures in the cells of the infiltrate, karyorrhexis and phagocytosis of nuclear debris are common. If many sections are examined, parts of the insect or arachnid may be found (Fig 50) In absence of this confirmatory evidence diagnosis may be difficult. The lesions showing pseudoepitheliomatous hyperplasia may be confused with



Fig 52 Bromod rma Lesion on low r leg (W U neg 50 1242)

Fig 53 —Bromoderma Hyperkeratosis acanthosis papillomatosis and pseudoepitheliomatous hyperplasia in the epid rmis A dense inflammatory cellular infiltrate in the dermis (W U neg 5 4318)

of the elbows and the palms of the hands. The etiology is unknown. Tuberculosis has been suggested as an etiologic factor but the evidence is inconclusive. Ellis considers lichen nitidus to be closely related to lichen planus

Histologically circumscribed groups of inflammatory cells occur immediately beneath the epidermis in the papillary layer of the dermis (Fig 51) They compress the epidermis above them and the rete ridges at the periphery of the lesion grow downward and, as Lever described the picture seem to clutch the infiltrate in the manner of a claw clutching a ball This infiltrate is made up of lymphocytes and histiocytes and a few Langhans giant cells. There is no true tubercle formation and no caseation necrosis



Fig 51 —Lichen nitidus. A small granuloma in the papillary portion of the dermis which has compressed the epidermis above it. (×270) (W U neg 52-4505)

Diseases of Metabolism

Bromoderma.—Drugs may cause many types of skin lesions which mimic cutaneous diseases occurring as idiopathic entities such as urticaria erythema nodosum, exfoliative dermatitis, and purpura. However the prolonged ingestion of bromides produces in susceptible persons verrucous, granulomatous pustular lesions often located on the extremities (Fig 52) Ingestion of iodides may produce similar lesions

In tissue sections of such lesions the epidermis shows hyperkeratosis, acanthosis and papillomatosis (Fig 53) The distortion and irregular downward proliferation of the epidermis produces the picture of pseudoepitheliomatous hyperplasia. Intraepithelial abscesses occur In the dermis a dense inflammatory cellular infiltrate is present which is made up of polymorphonuclear leukocytes, lymphocytes, histiocytes, and plasma cells. Abscesses are often scattered through the in



Fig. 52.—Bromoderma. Lesion on lower leg. (W. L. neg. 50-1..4..)

Fig. 53.—Bromoderma. Hyperkeratosis, acanthosis, papillomatosis, and pseudoepitheliomatous hyperplasia in the epidermis. A dense inflammatory cellular infiltrate in the dermis. (W. L. neg. 52-4318.)

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in the areas of necrobiosis. These droplets stain a rusty brown, which is the characteristic color that cholesterol stains with the Sudan dyes. Neutral fat such as that in the sebaceous glands stains a bright orange red. Hildebrand has shown that there is a preponderance of phospholipids and free cholesterol in these lesions. The microscopic picture of necrobiosis lipoidica diabeticorum resembles that of granuloma annulare, but in granuloma annulare there are no obliterative changes in the blood vessels and no lipid material in the lesion. Deposits of mucin are usually present in the areas of degenerated collagen in granuloma annulare.

Xanthoma. Xanthoma is caused by a disturbance in lipid metabolism. The clinical types are varied, and distinction between them is important from the standpoint of treatment and prognosis, but the microscopic picture is essentially the same in all types. Moore defines primary xanthomatosis as the deposition of cholesterol

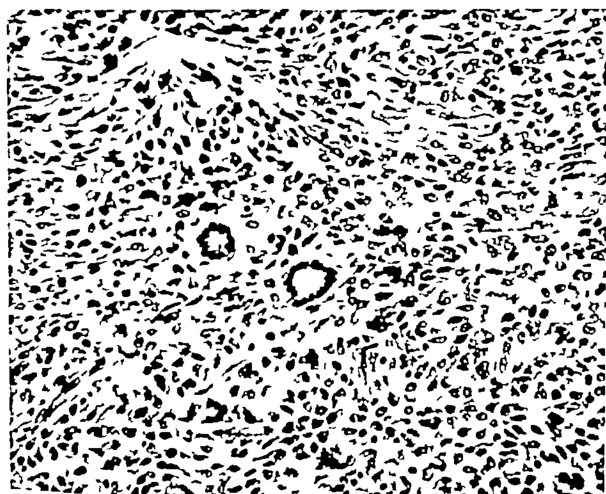


Fig. 56.—Photomicrograph of juvenile xanthogranuloma. Touton giant cells and prominent fibroblastic and reticuloendothelial proliferation. (×350.) (W.U. neg. 57-4624A.)

in cells in the form of tumor nodules and secondary xanthomatosis as the deposition of cholesterol in individual cells of a pre-existent disease. Some patients with the primary type show a hypercholesterolemia, while in others the serum cholesterol is normal. The secondary type is associated with a hyperlipemia. *Xanthoma tuberosum* and *xanthoma disseminatum* are skin lesions of primary xanthomatosis and *xanthoma diabeticorum* is an example of a skin lesion of secondary xanthomatosis which occurs in persons with diabetes.

filtrate. The dermis is edematous and blood vessels are dilated. Although the microscopic picture is not specific, a biopsy specimen is useful in ruling out such diagnoses as squamous carcinoma and blastomycosis which may be made clinically.

Necrobiosis Lipoidica Diabeticorum.—Clinically the lesions of necrobiosis lipoidica diabeticorum are sharply outlined, irregularly shaped sclerotic plaques. They are yellow in the center and have a violaceous halo at the periphery. They are found chiefly on the lower extremities and 80 to 90 per cent of the lesions occur in persons with diabetes. The disease is much more common in women. In 18 to 25 per cent of the cases reported by Hildebrand the skin lesions preceded by as long as eight years the onset of the symptoms of diabetes. The disease may be a local lipoid disturbance in the skin based on a general disturbance of fat metabolism. The lesions increase gradually in size and multiple lesions may coalesce. In old lesions the center may become atrophic and depressed.

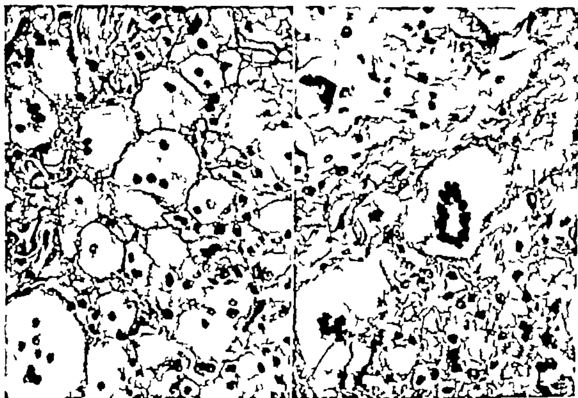


Fig 54.—Xanthoma. Foam cells or xanthoma cells containing lipid droplets in the cytoplasm. (×400.) (W U neg 51-452.)

Fig 55.—Touton giant cells in xanthoma. (×400.) (W U neg 51-451.)

On histologic examination irregular areas of necrobiosis of the collagen are conspicuous in the dermis. In these areas the collagen bundles show homogenization, swelling and degeneration and there is loss of elastic tissue. About these necrobiotic foci a perivascular inflammatory cellular infiltrate is present which is made up of histiocytes, lymphocytes, plasma cells, fibroblasts and an occasional foreign body giant cell. Obliterative changes in the blood vessels vary from endothelial proliferation to thrombosis. The changes in the vessels explain the necrobiotic areas in the collagen. Fat stains show extracellular droplets of lipid material

in the areas of necrobiosis These droplets stain a rusty brown which is the characteristic color that cholesterol stains with the Sudan dyes Neutral fat such as that in the sebaceous glands stains a bright orange red Hildebrand has shown that there is a preponderance of phospholipids and free cholesterol in these lesions The microscopic picture of necrobiosis lipoidica diabeticorum resembles that of granuloma annulare but in granuloma annulare there are no obliterative changes in the blood vessels and no lipid material in the lesion Deposits of mucin are usually present in the areas of degenerated collagen in granuloma annulare

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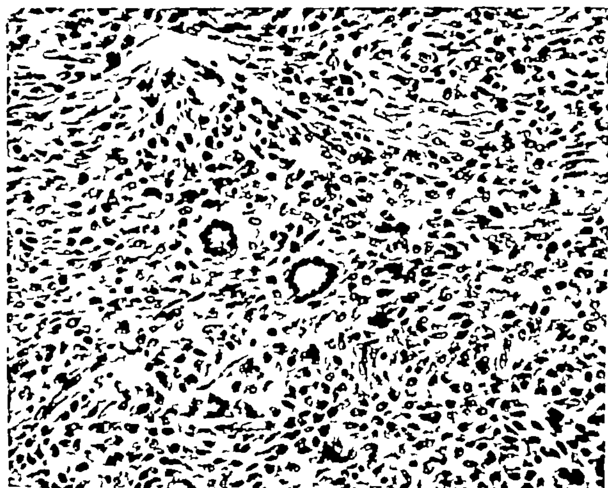


Fig 56.—Photomicrograph of juvenile xanthogranuloma. Touton giant cells and prominent fibroblastic and reticuloendothelial proliferation. (×350) (W U neg 57-4624A.)

in cells in the form of tumor nodules and secondary xanthomatosis as the deposition of cholesterol in individual cells of a pre-existent disease. Some patients with the primary type show a hypercholesterolemia while in others the serum cholesterol is normal. The secondary type is associated with a hyperlipemia. *Xanthoma tuberosum* and *xanthoma disseminatum* are skin lesions of primary xanthomatosis and *xanthoma diabeticorum* is an example of a skin lesion of secondary xanthomatosis which occurs in persons with diabetes

All of the xanthomatous lesions of the skin are yellow papules, nodules, or aques. On microscopic examination masses of foam cells or xanthoma cells are und in the dermis These cells are histiocytes which have one or more small yperchromatic nuclei and in their cytoplasm, small phagocytized lipid droplets. n routine sections in which the fatty material has been dissolved out, the cytoasm of these cells has a foamy appearance (Fig 54) The lipid material can be emonstrated in frozen sections stained with one of the Sudan dyes. It usually ains a rusty red because the lipid substance in xanthoma cells is predominantly olesterol. On polariscopic examination of frozen sections the lipid droplets are oubly refractile. Together with the foam cells there are a variable number of outon giant cells (Fig 55) These cells show a central mass of nonfoamy cytolasm encircled by a ring of nuclei and about the nuclei like a ruffle is a zone f foamy cytoplasm.

In early lesions some inflammatory cells lymphocytes polymorphonuclear ukocytes and histiocytes are present among the foam cells. In late lesions the am cells are replaced by fibrosis, and cholesterol clefts may be seen

Juvenile Xanthogranuloma (Nevoxanthoendothelioma)—This condition is haracterized by the appearance at birth or infancy of one or more tan to yellow rown asymptomatic, 1 to 15 mm. elevated nodules located most commonly about e head and neck but occasionally also on the trunk and extremities. Blood olesterol levels are normal. The lesions undergo spontaneous involution within x months to a few years.

Fig 56 shows a nodule which extends from just beneath the epidermis into e deep dermis or subcutaneous tissue. The cells are elongated or polygonal pparently histiocytic in type and usually contain fat Variable numbers of multi ucleated giant cells, often of Touton type, are interspersed throughout. Some f the giant cells are not typically Touton and these have been mistakenly attributed to be of endothelial origin.

One unfortunate complication has been encountered. Occasionally an infant ay develop unilateral glaucoma and a visible intraocular mass due to xanthoranuloma within the iris and ciliary body which obstructs aqueous outflow through e canal of Schlemm. Thus, the eye may be enucleated for suspected malignant umor This would be particularly likely in such an instance as that reported y Blank in which the eye lesion occurred several months before any skin lesions.

Helwig has reported an infant with juvenile xanthogranuloma who died and t autopsy was found to have extensive cutaneous lesions as well as lesions within ne testis and lung This further substantiates the fact that the lesions may be xtracutaneous as well as within the skin.

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TUMORS

INTRODUCTION

Both benign and malignant tumors of the skin arise from the cells of the epidermis the dermis or the skin appendages. Of their many forms only the most important are discussed here. Beerman's review indicates the scope of the literature

Carcinoma of the skin in the United States particularly in the southern states, is the commonest neoplasm. It occurs most often in out-of-door workers, more frequently in blondes than in brunettes. Its development is probably related to sunlight (Blum) In a few instances it is related to occupational trauma (Downing) occurs in burn scars as epidermoid carcinoma (Treves) arises in chronic draining sinuses secondary to osteomyelitis (McAnally) or to war wounds (Gillis) Both epidermoid carcinoma and basal cell carcinomas may follow previous irradiation therapy (Brown) Carcinoma of the skin frequently arises from the lesion known as senile keratosis but practically never from seborrheic keratosis.

Subepidermal Nodular Fibrosis (Dermatofibroma, Xanthoma, Sclerosing Hemangioma)

Subepidermal nodular fibrosis is discussed here because of its frequent confusion with malignant neoplasms It occurs usually on the exposed surfaces such as the extensor surfaces of the legs and may well be related to trauma (Fig 57) This lesion is usually no more than 2 cm. in diameter but we have seen it as large

as 6 cm It is firm nonulcerated arises in the dermis and has rather poorly defined margins. Because of contained fat it is yellow Microscopically it often is a highly cellular lesion with a complicated abundant vascular network (Fig 58) Because of its vascularity, Gross named it sclerosing hemangioma Large amounts of hemosiderin pigment in some of these lesions may be mistaken for melanin and

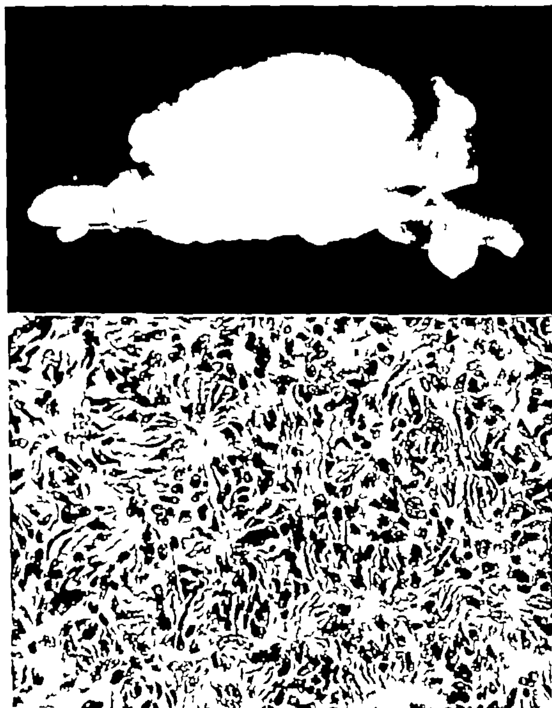


Fig 57 —Gross photograph of subepidermal nodular fibrosis arising in the skin of the leg beneath the uninvolved epidermis on the skin of the leg It was a bright yellow color (W U neg 52 1597) (Specimen contributed by Dr John Saxton St. Louis Mo)

Fig 58 —Photomicrograph of a cellular subepidermal nodular fibrosis. There was considerable fat present Individual cells show no mitotic activity (×400) (W U neg 48-5922.)

cause an incorrect diagnosis of melanocarcinoma. The epidermis shows increased melanin pigment in about 10 per cent of these lesions. The excessive fibrous tissue proliferation may result in an incorrect diagnosis of fibrosarcoma. Mitotic figures are rare. At times the large amounts of fat may cause it to be called a xanthoma. All these names have been combined under the all inclusive designation of *subepidermal nodular fibrosis* (Rentiers) *The treatment is excision.*

Keloids are tumorlike overgrowths of scar tissue which occur in predisposed persons, particularly Negroes, following trauma or surgical incisions of the skin (Fig 59) Early these lesions are often vascular and may be controlled by small amounts of irradiation. When they become extensive and highly fibrotic, removal may be successful but the recurrence may prove larger than the original lesion

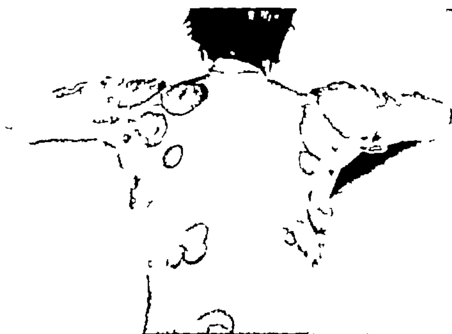


Fig 59 —Clinical photograph of extensive keloid formation in a Negro woman.

Seborrheic and Senile Keratosis

Seborrheic keratosis is a sharply circumscribed, usually elevated lesion covered by a loose steatoid horny layer Its color varies from yellow to brownish black (Fig 60) It is usually about 1 cm. in diameter but may reach several centimeters in size. Microscopically this lesion projects above the level of the epidermis (Fig 61) The epidermis is acanthotic, the basement membrane is intact and there are numerous horn cysts representing sections of papillae and hyperkeratotic follicles cut at various levels (Sachs) Basal cell carcinoma is said to develop in this lesion but we have not seen such an evolution in several thousand cases This lesion may be mistaken clinically for a malignant melanoma because of its intense melanin pigmentation (Becker)

Senile keratosis is directly related to sunlight and thus to out-of door occupations. Microscopically there is hyp parakeratosis, and

slight disorganization of the cells of the epidermis Epidermoid disorganization varies from focal atypical change to epidermoid carcinoma in situ and invasive carcinoma These changes are particularly well seen in lesions of the skin of the face and dorsum of the hand in farmers (Johnson) (Figs 62 and 63)

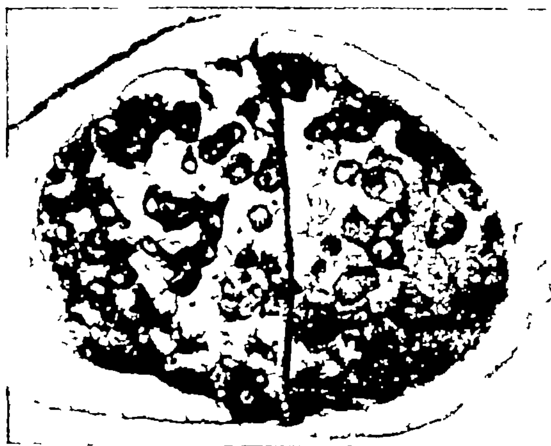




Fig 60 Large deeply pigmented, sharply circumscribed elevated seborrheic keratosis. (W U neg 49-6197)

Fig 61 Photomicrograph of seborrheic keratosis projecting above the level of the epidermis Note the numerous cysts representing sections of papillae and hyperkeratotic follicles cut at various levels (Low power) (W U neg 49 5195)

Irradiation Effect

The late effects of radiotherapy on treated tissues vary with dose and filtration. With well planned irradiation for a radiosensitive tumor the amount of irradiation necessary to sterilize the tumor is much less than the amount which causes irreversible changes in the normal tissue The surrounding skin reverts nearly to normal after such irradiation If the irradiation is poorly planned (excessive dosage and little or no filtration) permanent sequelae occur These same altera

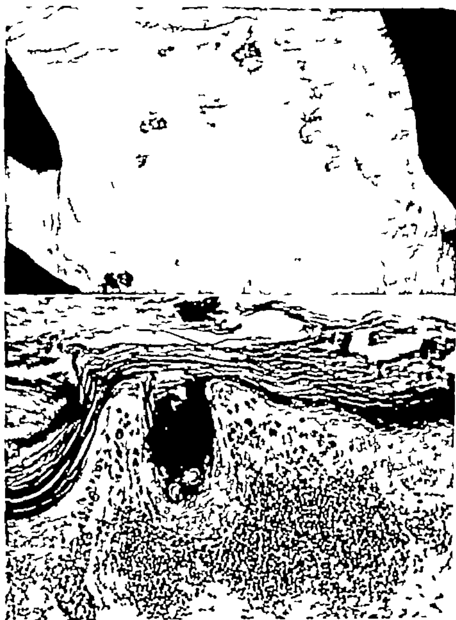


Fig 62 —Clinical photograph of numerous senile keratoses on the dorsum of the hand. Clear area in the center represents previous zone of excision with replacement by skin graft. (W U neg. 49-1887) (From Johnson, R., and Ackerman L. V Cancer 3: 657 1950)

Fig 63 —Photomicrograph of a senile keratosis with focal atypical changes in the epidermis. This is the type of lesion which progresses to invasive epidermoid carcinoma (×210) (W U neg. 49-4198) (From Johnson, R., and Ackerman L. V Cancer 3: 657 1950)

tions may occur if there is a narrow margin between the amount of irradiation necessary to sterilize a given tumor and the amount causing permanent skin damage. Permanent alterations also occur in patients who have had ill conceived therapy for acne or other skin lesions. Under these conditions, the skin is thin hairless and often telangiectatic. The microscopic section shows atrophy of the epidermis increased pigmentation of the basal layer, absence of all skin appendages dilatation of the blood vessels and fibrosis (Fig 64)



Fig 64.—Photomicrograph of irradiation effect of skin. Note absence of all skin appendages (Low power) (W U neg 49 5444)

Endarteritis is rare in the absence of necrosis. Such profoundly altered skin may undergo radionecrosis with ulceration after slight trauma. In time hyperkeratotic areas appear which may be followed by epidermoid carcinoma or rarely basal cell carcinoma. The only logical treatment is replacement of the altered skin with skin grafts before epidermoid carcinoma supervenes. Epidermoid carcinoma occuring in such an area cannot be treated by irradiation because of the very poor strata in which it is growing. It must be excised

BASAL CELL AND EPIDERMOID CARCINOMA

Two important common types of skin carcinoma are the basal-cell carcinoma and the epidermoid carcinoma. They have definite differences both clinically and microscopically. Grossly their differentiation may be easy or difficult.

Epidermoid carcinomas are prominent on the dorsum of the hands the ears, and the temples. Basal cell carcinomas are by far the most common on the nose,

skin of the upper and lower lips chin and eyelids (Fig 65) Both of these carcinomas occur most often on the exposed surfaces (Fig 66) Both can occur in scars. Epidermoid carcinoma almost always is the lesion arising in burn scars, draining sinuses or in areas of irradiation Rarely basal cell carcinoma occurs

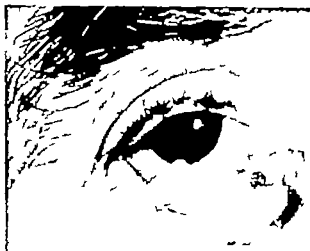


Fig 65 — Clinical photograph of a rather large basal cell carcinoma *of the lower eyelid.* (*W U neg 50-3089*)



Fig 66. —Clinical photograph of a large ulcerating epidermoid carcinoma of the preauricular area. (Courtesy Dr Henry Schwartz, Columbia, Mo EFSCH 14699)

in irradiated areas. Epidermoid carcinoma may metastasize, particularly after *faulty treatment of a deeply invasive lesion* Epidermoid carcinomas on the dorsum of the hand growing below the level of the sweat glands (Johnson) or arising from the ear most often metastasize. Lymph node metastases occurred in

52 (11 per cent) of 411 epidermoid skin cancers which were followed for a five year period at the Ellis Fischel Cancer Hospital. All but 10 of the 52 primary lesions which exhibited metastases were larger than 2 cm in diameter, and in 30 of the 52 there had been previous unsuccessful treatment. Thus metastases from epidermoid skin cancer are prone to occur after the lesion has attained a large size or has been inadequately treated (Modlin). Basal cell carcinomas practically never metastasize (Lattes).

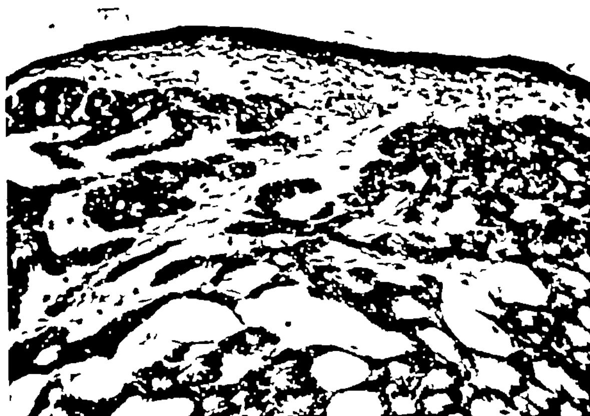


Fig 67.—Photomicrograph of a basal cell carcinoma with cystic changes, often designated as the adenoides cystica type (×210) (W U neg 49 3319)

Grossly basal cell carcinoma may range from a small pearly elevated nodule to a destructive lesion which can erase half the face and destroy bone and cartilage. It is easily recognized when it is characteristically located and appears as a small translucent gray nodule with delicate veins over the surface. At times it may be mistaken for a malignant melanoma because of excessive melanin production (Cipollaro). If it is of the adenoides cystica type it may be mistaken clinically for a benign cyst.

Microscopically basal cell carcinoma has various patterns. The different patterns include focal areas of keratinization, cystic changes with fluid formation pigmentation and sebaceous differentiation (Fig 67). We feel that a classification has no practical value (Lennox).

Basosquamous carcinoma is often designated as a particular form of skin carcinoma. This designation was reserved for carcinomas in which a portion of the tumor resembled basal cell carcinoma, and another a squamous carcinoma the implication being that the squamous element could metastasize. The designation

of tumors as basosquamous depends on the mood of the pathologist. We rarely make this diagnosis at present. Practically all of these lesions are basal cell carcinomas and behave as such. In no instance at the Ellis Fischel State Cancer Hospi

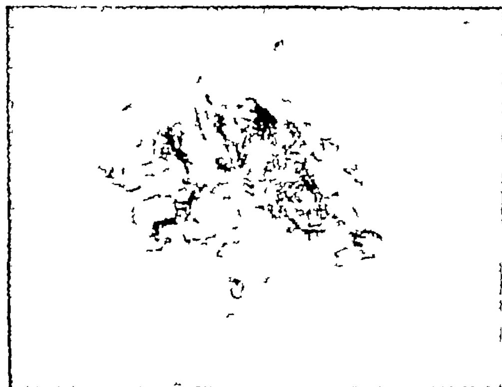


Fig 68. Ulcerating destructive epidermoid carcinoma growing in an ancient burn scar (W L neg 48-5569)

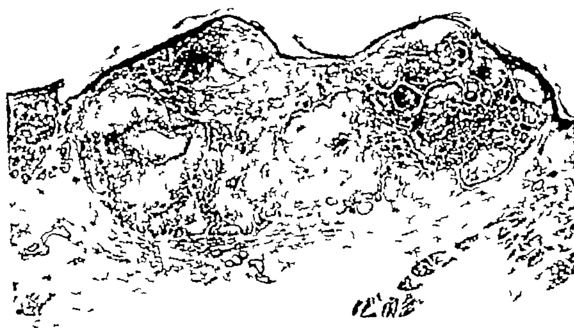


Fig 69.—Adequate excision of an ap cial basal cell c te its deep extensio r 49-5943.)

tal did a basosquamous carcinoma metastasize Certain carcinomas particularly if undifferentiated or previously irradiated cannot be accurately classified

Epidermoid carcinoma of the skin is usually well differentiated, containing epithelial pearls and clearly defined intercellular bridges This tumor slowly invades the underlying tissues and if neglected becomes a very large ulcerating mass.

The microscopic recognition of these common skin cancers should not be difficult The basal cell carcinoma has uniform cells small nuclei little cytoplasm and often palisaded cells on its margins The formation of cystic spaces should occasion no difficulty in recognition A postirradiation persistent basal cell carcinoma may show prominent nuclei and nucleoli abundant cytoplasm and cells which are somewhat spindle shaped Recognition at this time may be difficult. The *epidermoid carcinoma* is easily recognized except when highly undifferentiated when there is no evidence of keratinization and no intercellular bridges. Multiple sections may show small areas of keratinization The individual cells of the squamous carcinoma have prominent well-defined nuclei prominent nucleoli and a somewhat glassy cytoplasm Both of these tumors unfortunately can be mimicked quite successfully by a relatively nonpigmented melanocarcinoma

Clinicopathologic Correlation

Both basal cell and epidermoid carcinoma can be treated successfully by a well trained surgeon or radiotherapist Only 17 (2 per cent) of 808 patients with *basal cell carcinoma followed for a five year period at The Ellis Fischel Cancer* Hospital died of cancer In this group there were 123 recurrences following initial treatment but 107 of these were controlled The figures for epidermoid carcinoma (often advanced) were not nearly as good 59 (22 per cent) of 303 died of cancer (Modlin) Irradiation is best suited for lesions previously untreated in which excision would necessitate mutilation or tedious plastic repair (carcinomas around the eye or on the nose) (Regato) Excision is the treatment of choice in areas where deformity does not result It is indicated for lesions which have persisted after irradiation or which grow in areas that tolerate irradiation poorly Thus carcinomas in a burn scar or an irradiation scar or in the atrophic skin of the dorsum of the hand are best treated by excision (Fig 68) Both the surgeon and the radiotherapist at times are not aware of the depth of infiltration of the basal cell carcinoma It is not rare for a wide excision to be too superficial to include the deep infiltration of the tumor (Fig 69) In this regard it is important that the surgeon inform the pathologist of the specimen's orientation so that proper sections can be made to show whether or not the excision is adequate. If the excision is inadequate more extensive surgery should in many instances await clinical evidence of persistent cancer

BOWEN'S DISEASE

Bowen's disease of the skin is a clinical diagnosis The lesions are superficial are salmon pink in color and have slightly elevated margins (Figs 70 and 71) They are seen commonly on the posterior chest and occasionally on the face Often they are mistaken for other skin conditions Biopsy reveals noninvasive epidermoid carcinoma (Fig 72) This lesion should not be confused with epi

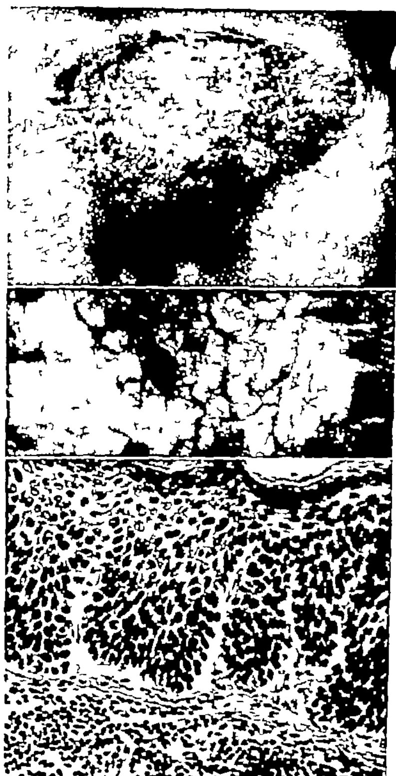


Fig 70.—Clinical photograph of Bowen's disease located just above the anus in a Negro (W U neg 49-5915)

Fig 71 —Detailed view of the margin of the lesion shown in Fig 70 (W U neg 49-5916.)

Fig 72.—Photomicrograph of epidermoid carcinoma in situ Note total disorganization of all layers with innumerable mitotic figures. (High power) (Contributed by Dr Zola Cooper St. Louis Mo)

dermoid carcinoma in situ when it occurs in arsenical keratoses or irradiated (Herold) It can be treated by irradiation or excision

SPECIFIC TUMORS ARISING FROM SKIN APPENDACES

Benign and Malignant Tumors of Sweat Gland Origin

Benign tumors of sweat gland origin are of several types The so-called *r tumor* of the skin which resembles mixed tumors of salivary gland origir doubtedly arises from sweat glands. It is found on both exposed and unex surfaces is most frequently seen on the face, but is not unusual in the palma plantar skin (Simard) It grows beneath the surface of the epidermis and cystic areas often lined by a double layer of cells (Fig 73) The presence of lage is common (Fig 74) It is not often larger than 3 cm in diameter I experience this tumor is practically never malignant We know of one ins of recurrence (Ahlbom) Mucin secretion can occur (Lennox)

The hidroadenoma is a tumor arising from apocrine sweat glands (McDo (described in the chapter on the Female Reproductive System under Vulv p 607) We have not seen these tumors become malignant. An adenor the apocrine sweat glands in the anal canal was mistaken initially for carci of the rectum invading the anus Cooper also has reported such a case The I adenoma arises from the epithelium of the apocrine glands A tumor desig as syringocystadenoma papilliferum arises from the ducts of the sweat g It is benign often is seen around the scalp and is associated with papillary fo tions of duct epithelium which block the ducts and cause chronic inflammati

The *syringoma* is a benign tumor of sweat gland origin occurring in during puberty These lesions form soft yellowish nodules of pinhead size i skin of the eyelid, chest abdomen and anterior aspect of the thighs (L Microscopically there are numerous small cystic ducts lined by two layers of At times there are commalike projections of these ducts (Fig 75) The apo gland origin of these tumors is supported by the occasional observation of secretion. These lesions are entirely benign.

The *turban tumor* so designated because of its tendency to form innume tumor nodules on the scalp back, and arms is thought by many to arise sweat glands (Sutherland) The tumors grow beneath the intact epidermi form resilient nodules which may become several centimeters in diameter (chese) (Fig 76) Microscopically they show characteristic hyaline areas rounded by small deeply blue-staining cells (Fig 77) They do not metast They respond poorly to irradiation and should be treated by excision.

Stout has emphasized that *apocrine sweat gland cancers* slowly form pur red elevated nodules (Fig 78) These tumors microscopically are pap and resemble apocrine epithelium (Fig 79) They tend to recur and may ev ally metastasize or involve underlying structures such as bone (Horn) The mon sites of origin are the axilla, the scrotum, and the vulva. Keasbey h sweat gland carcinomas with metastases in her group of 235 sweat gland tu She also reported 3 carcinomas of sweat glands under the title of clea hidradenoma"

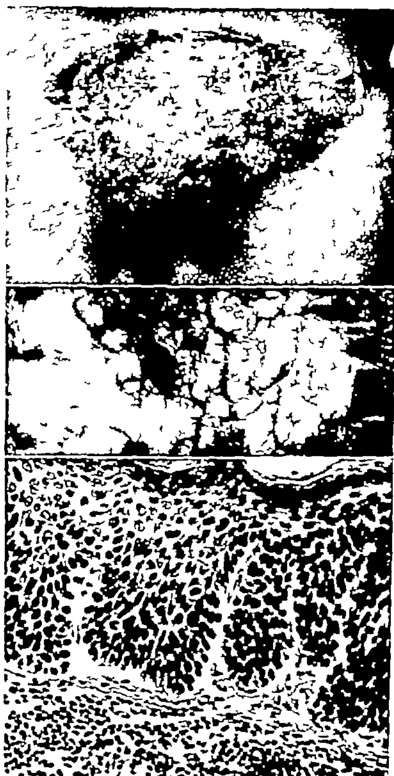


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Benign tumors of sweat gland origin are of several types. The so-called *mixed tumor* of the skin which resembles mixed tumors of salivary gland origin undoubtedly arises from sweat glands It is found on both exposed and unexposed surfaces is most frequently seen on the face, but is not unusual in the palmar and plantar skin (Simard) It grows beneath the surface of the epidermis and shows cystic areas often lined by a double layer of cells (Fig 73) The presence of cartilage is common (Fig 74) It is not often larger than 3 cm. in diameter In our experience this tumor is practically never malignant. We know of one instance of recurrence (Ahlbom) Mucin secretion can occur (Lennox)

The hidroadenoma is a tumor arising from apocrine sweat glands (McDonald) (described in the chapter on the Female Reproductive System under Vulva, see p 607) We have not seen these tumors become malignant. An adenoma of the apocrine sweat glands in the anal canal was mistaken initially for carcinoma of the rectum invading the anus. Cooper also has reported such a case. The hidroadenoma arises from the epithelium of the apocrine glands. A tumor designated as syringocystadenoma papilliferum arises from the ducts of the sweat glands. It is benign, often is seen around the scalp and is associated with papillary formations of duct epithelium which block the ducts and cause chronic inflammation.

The *syringoma* is a benign tumor of sweat gland origin occurring in girls during puberty These lesions form soft yellowish nodules of pinhead size in the skin of the eyelid chest, abdomen and anterior aspect of the thighs (Lever) Microscopically there are numerous small cystic ducts lined by two layers of cells. At times there are commalike projections of these ducts (Fig 75) The apocrine gland origin of these tumors is supported by the occasional observation of active secretion. These lesions are entirely benign

The *turban tumor* so designated because of its tendency to form innumerable tumor nodules on the scalp back, and arms, is thought by many to arise from sweat glands (Sutherland) The tumors grow beneath the intact epidermis and form resilient nodules which may become several centimeters in diameter (Ronchese) (Fig 76) Microscopically they show characteristic hyaline areas surrounded by small deeply blue staining cells (Fig 77) They do not metastasize. They respond poorly to irradiation and should be treated by excision.

Stout has emphasized that *apocrine sweat gland cancers* slowly form purplish red elevated nodules (Fig 78) These tumors microscopically are papillary and resemble apocrine epithelium (Fig 79) They tend to recur and may eventually metastasize or involve underlying structures such as bone (Horn) The common sites of origin are the axilla, the scrotum and the vulva. Keasbey had 8 sweat gland carcinomas with metastases in her group of 235 sweat gland tumors She also reported 3 carcinomas of sweat glands under the title of "clear-cell hidradenoma"

Dermoid Cysts, Sebaceous Cysts, Epidermal Inclusion Cysts, and Sebaceous Gland Carcinoma

Dermoid cysts, sebaceous cysts and epidermal inclusion cysts are almost always diagnosed as sebaceous cysts. However they can be distinguished both



Fig 73.—Photomicrograph of a so-called mixed tumor of the skin which did not involve the epidermis. Note glands lined by a double layer of cells. (×200) (W U neg. 49-4542)

Fig 74.—Photomicrograph of another area of the tumor shown in Fig 73 demonstrating formation of cartilage. (×200) (W U neg 49-4543)

clinically and pathologically The dermoid cyst is rare and occurs in the region of embryonic cleavage lines such as in the skin of the temple and the midline of the neck. These benign cysts are lined by stratified squamous epithelium and may

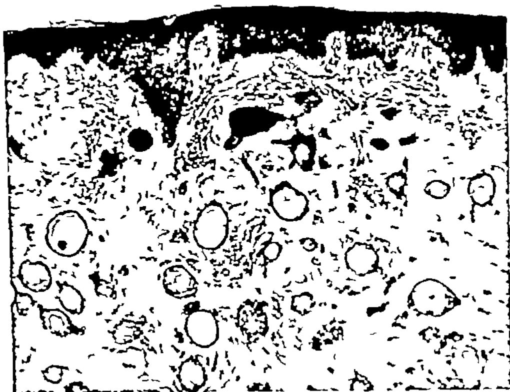


Fig 75—Syringoma a benign tumor of sweat gland origin forming cystic ducts lined by two layers of cells some of which show a commalike projection. (×135) (W U neg 52 4548.)

Fig 76—Innumerable tumors involving the scalp demonstrating the reason for calling this a turban tumor (Courtesy Dr Juan del Regato Colorado Springs Colo)

Fig 77—Photomicrograph of a turban tumor with the typical hyaline areas ringed round by well-differentiated cells. (×600) (W U neg 52-4597)

contain hair They are monodermal (ectoderm) in origin. True sebaceous cysts are lined by sebaceous cells which are an integral part of the lining wall (Warvi) (Fig 81) The epidermal inclusion cyst by far the most common, is undoubtedly related to traumatic displacement of epidermis into the deeper layers of the skin (Fig 80) Sebum is produced and collects within the keratinized cyst wall It may escape through a sinus in the dimpled overlying skin. On section these cysts contain inspissated sebum having the odor and consistency of fetid cottage cheese. At times foreign body giant cell reaction may be prominent within them

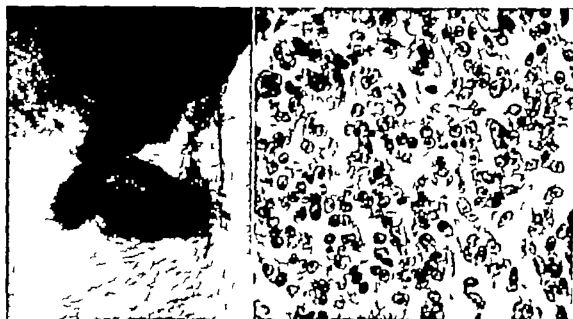


Fig. 78—Clinical photograph of an elevated purplish red carcinoma arising from the apocrine glands of the axilla in a male. (From Ackerman L. V and del Regato J A. Cancer St. Louis 1947 The C. V Mosby Co)

Fig 79—Photomicrograph of the apocrine gland carcinoma shown in Fig 78. Note fairly well-differentiated pattern and resemblance to apocrine glands This lesion recurred after surgery and finally metastasized causing the death of the patient several years after its onset. (×600) (W U neg 52-4396)

Epidermoid carcinoma practically never develops within either a true sebaceous cyst or an epidermal inclusion cyst. Occasionally these cysts become filled with proliferating well-differentiated squamous epithelium forming epithelial pearls (Fig 82) This lesion in the past, was considered epidermoid carcinoma (Fig 83) However follow-up shows that such lesions are not malignant and do not metastasize. Lund designates this condition as subepidermal acanthoma.

KERATOACANTHOMA (MOLLUSCUM SEBACEUM)

This benign lesion of the skin (arms face and chest) is derived from squamous epithelium. It occurs at any age and has a rapid growth rate from a small papule to its full size in a six to eight week period. It then regresses over a variable period, leaving a small scar This lesion which may be multiple, has been called primary self healing prickle cell epithelioma and squamous carcinoma of the skin (Witten)



Fig 80 —Epidermal inclusion cyst of the skin showing communication with the over lying surface It is lined by stratified squamous epithelium. (Low power) (W U neg 51-4670)

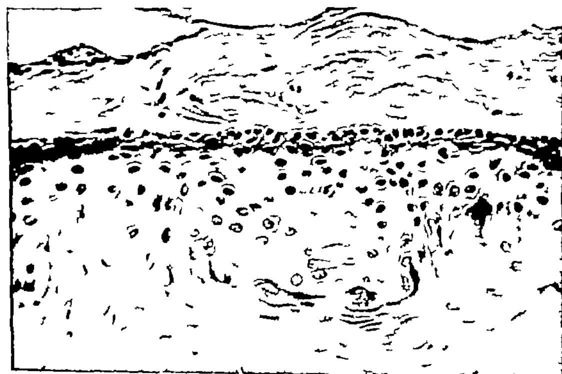


Fig 81 — True sebaceous cyst lined by sebaceous cells (×420) (W U neg. 52-4546)





Fig 82.—Gross photograph of a large sebaceous cyst of the skin of the arm. Note retracted dimple on the surface with the cyst filled with keratinized material. (W U neg. 53 1806.)

Fig 83.—Photomicrograph of well-differentiated squamous epithelium filling the cyst shown in Fig 82. This is not epidermoid carcinoma. (×112.) (W U neg 58-238.)

Grossly and microscopically keratoacanthoma has a distinctive pattern, there is a central crater filled with keratin (Bowman) (Figs 84 and 85) Microscopically it is cup shaped with well-defined borders of well-differentiated squamous epithelium. We have incorrectly diagnosed this lesion in the past as a well-differentiated carcinoma (Brown) but if the criteria above is used this error should never be made.





Fig 84—Gross photograph of a keratoacanthoma of the skin with a central crater filled with keratin. (W U neg 58-3442)

Fig 85—Photomicrograph of a keratoacanthoma with sharply demarcated margins cup shaped, and central crater filled with keratin. (×15) (W U neg 57 5803)

KAPOSI'S DISEASE

Kaposi's sarcoma is a malignant lesion of slow evolution in adults its progression is more rapid in children. It is said to be more common in Italian and Jewish males The usual age of occurrence is between 50 and 70 years It frequently

begins on the lower extremities where it may be preceded by edema. Individual maculopapular lesions are less than 1 cm. in diameter Single lesions however, *may be elevated and exactly simulate a pyogenic granuloma (Fig 86)* Because of the dark color and multiplicity of the lesions, we have seen this disease mistaken clinically for a malignant melanoma in the lower extremity Microscopically the earliest changes may be difficult to evaluate, for the lesions are often quite vascular with little evidence of a sarcomatous stroma (Fig 87) With the passage of time the diagnosis becomes more obvious as sarcomatous stroma develops and vascularity diminishes (Fig 88) Origin may be from the reticuloendothelial system. The lesion may coexist with leukemia. These lesions show extreme radiosensitivity (McCarthy) We have seen them originate in the rectum oral cavity and lymph nodes or appear in the viscera without peripheral manifestations (Tedeschi) Eventually the patients die often from intestinal hemorrhages.



Fig 86.—Clinical photograph of Kaposi's sarcoma with innumerable elevated hemorrhagic lesions. (W U neg 48-4296.)

RARE TUMORS

Calcifying epithelioma of Malherbe occurs usually in children, most frequently in the region of the head. The lesion is small and single and covered by intact skin (Puente Duany) Microscopically it is made up of globular masses of basophilic cells surrounded by a vascular connective tissue capsule (Setala) (Fig 89) *Hyalinization cornification*, and calcification occur centrally Bone formation is rare. These benign tumors are probably derived from the pilosebaceous apparatus. Excision is curative. They have to be differentiated from calcified epidermal cysts which do not contain basophilic cells (Lever)

Mycosis fungoides should be sharply separated from involvement of the skin in patients with Hodgkin's disease, lymphatic leukemia, and diffuse lymphosarcoma It is a slowly progressive malignant lymphoma of the skin which may

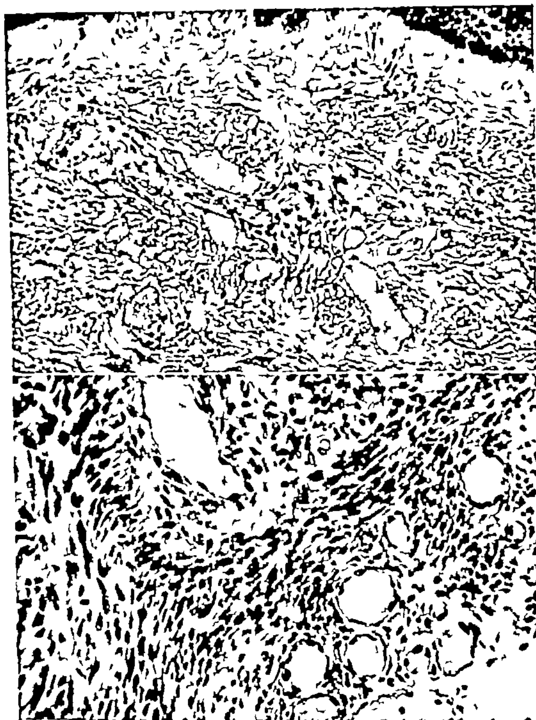


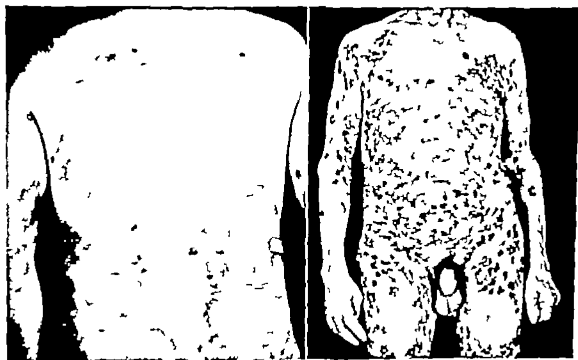
Fig 87—Early lesion of Kaposi's sarcoma. The extreme vascularity may cause this lesion to be incorrectly diagnosed. (×100) (W U neg 52 4544)

Fig 88—Well-developed Kaposi's sarcoma with diminished vascularity and sarcomatous stroma. (×400) (W U neg 52-4545)

take different forms. Early the skin may be thickened, diffusely reddened and without definite nodules. At this time a definite diagnosis usually is suspected but may be difficult to make microscopically (Fig 90) If there is nodula



Fig 89—*Calcifying epithelioma of Malherbe with globular masses of basophilic cells and* early central calcification. (×200) (W U neg. 48-6856.)



Figs. 90 and 91—Two photographs of a patient with mycosis fungoides separated by an interval of thirteen months. (Fig. 90 W U neg 50-5967 Fig 91 W U neg 51-6175)

tion with the formation of multiple nodules over the face, trunk, and other areas, biopsy will show definite malignant lymphoma (Figs 91 and 92) The diagnosis usually suggested will be reticulum cell sarcoma This disease probably takes origin from the reticuloendothelial system Frequently, however, the correct diagnosis may be *in doubt because of multinucleated cells suggesting* Reed Sternberg cells (Fig 93) The process is somewhat granulomatous, with histiocytes plasma cells, and fibroblastic proliferation (Winer) Cutaneous *involvement may last ten or* more years, finally terminating with visceral manifestations In 16 of 18 cases reviewed by Berman there were visceral manifestations. This lesion may respond to irradiation (Post)

There is a rare cutaneous lesion diagnosed best as a *lymphocytoma* which may be confused with lymphosarcoma (Mopper)



Fig. 92 —Extreme nodulation of the face due to mycosis fungoides (W U neg 49-6320)

Fig 93 —Photomicrograph of mycosis fungoides Note variation in pattern, but the dominant cell is the reticulum cell. This could be designated as reticulum cell sarcoma. (×600) (W U neg 52-4398)

METASTATIC TUMORS

Malignant tumors occasionally metastasize to the skin. Carcinomas of the breast and stomach are the most common primary sources of *cutaneous metastases.* Other primary lesions include those of the lung uterus thyroid bladder kidney

and pancreas (Gates) These lesions initially involve the dermis but may ulcerate the overlying epidermis. The metastatic tumor is sharply demarcated microscopically from the surrounding epidermis

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NEVI AND MALIGNANT MELANOMA

INTRODUCTION

The word nevus is usually used as a synonym for mole although by derivation the word nevus means mark. However common usage has made the two words synonymous, and the word nevus will be used here. The pathologic problems in the diagnosis of moles and melanoma include incorrect diagnosis of a cellular mole as malignant melanoma, incorrect diagnosis of an early malignant melanoma failure to appreciate the potentialities of the juvenile melanoma, failure to recognize nonpigmented forms of malignant melanoma, and muddy thinking regarding the origin of the mole

ORIGIN AND DISTRIBUTION

Masson's concept of dual origin of moles from intraepidermal melanoblasts and proliferation of dermal schwannian cells is supported by many studies The common mole has been demonstrated to have neuroectodermal origin by careful histologic study and particularly through special staining of neurites by the Cajal technique (Laidlaw Masson Berkheiser) Further the malignant melanoma of the skin is a radioresistant neoplasm as contrasted to the basal cell carcinoma and epidermoid carcinoma. We have seen heavily irradiated benign moles and malignant melanomas in which there has been little or no irradiation effect. Finally phylogenetic evidence strongly supports neural crest origin of melanoblasts (DuShane Laidlaw Rawles Willier) Every person has a variable number of moles. Their distribution is not the same as malignant melanoma they are much more common in the head and neck areas while malignant melanoma is much

more common in the lower extremity Nevi of every conceivable size shape, and degree of pigmentation occur they may be more or less hairy Nevi have been variously classified, but it is most logical to divide them according to the location of the neval cells inasmuch as their position bears a definite relationship to the type of nevus from which malignant melanoma arises The terminology of pigment cells associated with the formation of melanin pigment as used in biology and medicine has been confusing The recommended terminology is shown by Table 2 (Fitzpatrick)

TABLE 2 RECOMMENDED TERMINOLOGY OF PIGMENT CELLS*

Mature melanin forming cell	Melanocyte
Immature melanin forming cell	Melanoblast
Cell with phagocytized melanin	Macrophage (or melanophage)
"Contractile" cell	Melanophore

From Fitzpatrick T B and Lerner A B Science 117: 610 1953

TYPES OF NEVI

Junctional

A junctional nevus is one in which the neval cells are present at the dermal epidermal junction The intradermal nevus represents the nevus in which all the neval cells are in the dermis The combination of these two forms occurs and is designated by some as a compound nevus The percentage of nevi with junctional changes decreases as the age of the patient increases A review of 156 moles from children under 15 years of age showed 110 (70 per cent) to be junctional. Conversely 258 (80 per cent) of 312 moles from adults showed no evidence of junctional change (Ackerman) Furthermore Stegmaier demonstrated junctional activity in 100 consecutive moles in children below the age of 10 years These findings support Masson's concept of the gradual migration of the epidermal melanoblasts away from the epidermis Furthermore the schwannian elements in the dermis continue their proliferation (Masson) With increased age there is an increase of neuroid bundles and nervelike elements (Berkheiser) For some unexplained reason in adult life junctional nevi tend either to persist or appear in greater proportion in the lower extremity Although in adults only a small percentage of all nevi occur below the knee practically all of them are junctional in character Nevi are also common on both male and female genitalia However a survey of 14 nevi of the vulva showed only 2 to be junctional. Grossly the usual junctional nevus is a flat to slightly elevated, nonhairy fawn-colored area (Fig 94) Microscopically the junctional nevus is recognized by the presence of the neval cells growing in the region of the dermal-epidermal junction (Fig 95) The junctional nevus is the lesion from which many malignant melanomas arise.

Intradermal

The intradermal nevus is the common adult type nevus. It may be papillary pedunculated, or flat (Fig 96) Usually it is hairy and invariably is multiple. Its degree of pigmentation varies widely Malignant melanomas practically never arise from this type of nevus Microscopically the neval cells are entirely within

the dermis they are arranged in small nests or bundles may form pseudoacini, and have giant cells (Fig 97) Their extreme cellularity may result in an incorrect diagnosis of malignant melanoma (Fig 98) These nevi, like others show no evidence of circumscription. Nevi almost invariably arise in the skin but we have seen an intraepithelial nevus of the hard palate and the tonsillar area.

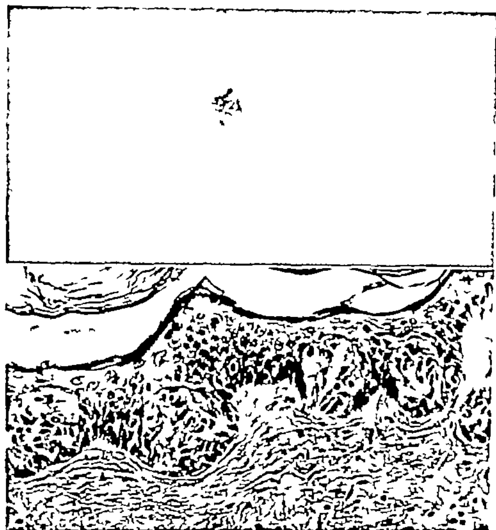


Fig 94 —Clinical photograph of a junctional nevus on the plantar surface of the foot. It was nonhairy and fawn colored. (W U neg 49 1492)

Fig 95 —Photomicrograph of a typical junctional nevus in an adult. Note the location of the cells at the dermal-epidermal junction. (High power) (W U neg 51-464)

Blue Nevus

The blue nevus is distinctive and is often suspected of being malignant because of its rather intense pigmentation. Helwig collected 192 cellular blue nevi 67 were in the region of the sacrum and buttock 73 on the dorsum of the feet ankles, and toes and 28 on the wrist, hands and fingers 155 were in males (Fig 99) There were metastases to regional lymph nodes in four instances these nodes and the primary tumor were excised. There were no further metastases and all four patients were living and well at the time of his report. Three had been followed for

over five years The draining regional lymph nodes may be intensely pigmented but this is not evidence of metastases since free melanin pigment in the region of the nevus may be carried to the nodes by the draining lymphatics Microscopically there are no neval cells at the dermal-epidermal junction, there is a clear space

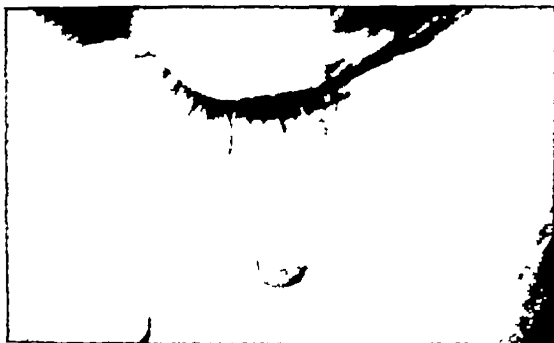




Fig 96—Clinical photograph of a typical intradermal nevus of the skin of the cheek (W U neg 49-169)

Fig 97—Photomicrograph of the nevus shown in Fig 96 with the cells arranged in small nests and bundles lying entirely within the dermis. (Low power) (W U neg 49-2024)

between the tumor and the epidermis (Montgomery) Fusiform cells, apparently melanocytes, containing melanin pigment grow diffusely in the dermis (Fig 100)

Unusual Nevi

In 1931 Masson reported a *giant neuronevus* of the hairy scalp The nevi from the scalp more frequently show neuroid elements in the dermis However

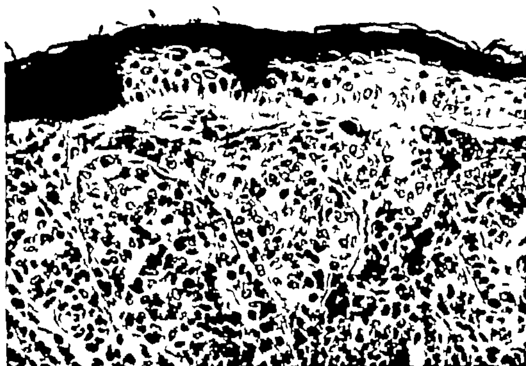


Fig 98—Photomicrograph of an excessively cellular intradermal nevus with occasional large cells. This is the type which may be incorrectly diagnosed as malignant. (High power) (W U neg 48-6693)



Fig. 99—Gross photograph of a large blue nevus occurring in the buttock. (W U neg 53 5790)



Fig 100 —Photomicrograph of a blue nevus. Note the fusiform cells in the dermis containing melanin pigment (Low power)

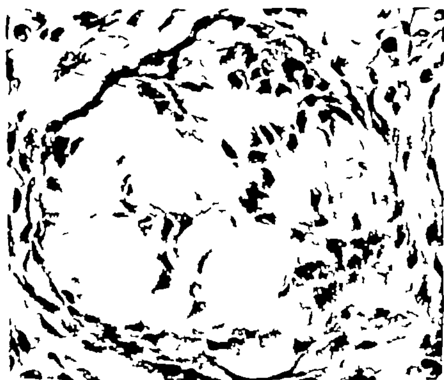


Fig 101 —Photomicrograph of Wagner Meissner corpuscle in a large neuronevus of the posterior chest in a child. (×600) (W U neg 52 243)



Fig 102.—Clinical photograph of large congenital hairy nevus on the skin of the face in a child. This type of lesion does not become malignant. (W U neg 47 5464)

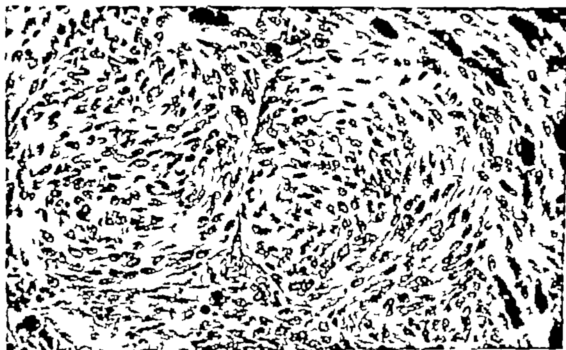


Fig. 103.—Photomicrograph of a large blue neuronevus of the buttock with whorllike areas and fusiform cells producing melanin pigment. (×380) (W U neg 52 141)

we have observed a large neuronevus composed almost entirely of Wagner Meissner corpuscles (Fig 101) in a 5 month-old child These nevi do not become malig nant Large congenital hairy nevi in children rarely may grow rapidly but despite such growth malignant change has not been observed (Fig 102) We have seen 15 cases of large heavily pigmented nevi occurring usually on the lower back or buttock which were difficult to interpret (Fig 103) These nevi show no changes in the epidermis the cells are fusiform and highly cellular and produce much melanin pigment The size deep pigmentation and cellularity frequently cause an incorrect diagnosis of malignant melanoma These lesions expand into rather than infiltrate the surrounding tissue Although cellular, the lesion shows practically no mitotic activity (Fig 103) We have not seen malignant change take place in this type Masson designates this lesion as a blue neuronevus.

Clinicopathologic Correlation

The congenital large hairy and disfiguring nevi have to be removed for cos metic purposes not because of the danger of malignant degeneration In fact the hairy nevus practically never becomes malignant (Affleck) Obviously all nevi cannot be removed because every adult has some ten or twenty If the nevus is chronically irritated by a belt collar strap or shoe it should be removed The signs of possible malignant change in a nevus include *deepening of pigmentation spread of the pigment beyond the gross confines of the lesion, ulceration and rapid growth*

Approximately 50 per cent of malignant melanomas arise from pre-existing nevi (Ackerman 1918) These nevi in practically all instances are junctional in nature (Traub Allen) However, junctional activity is to a great extent a func tion of age and development The appearance or enlargement of a junctional nevus in adults is probably indication for its removal It is our policy to recom mend removal of nevi below the knee particularly those in the region of the foot because practically all of them are junctional in nature These nevi should be removed with a cold knife (Webster) Even the most observant and astute surgeon cannot be certain that the nevus he is removing is not already a melanoma. All require histologic study

Although the cautery will not cause a perfectly benign intradermal nevus to become malignant the steam of cautery used on a malignant melanoma possibly drives cancer cells into open small venules and lymphatics leading to the develop-ment of satellite skin nodules (Amadon) Furthermore some consideration should be given to the poor pathologist. He has enough difficulty in the interpreta tion of borderline nevi without adding distortion of the tissue and peculiar stain ing reactions due to cautery Histologic interpretation of a cauterized specimen is extremely difficult if not impossible

MALIGNANT MELANOMA

Distribution

Malignant melanomas of the skin occur most frequently in the head and neck area and in the lower extremities (Table 3)

TABLE 3 HISTORY OF PRE-EXISTING MOLE IN MALIGNANT MELANOMA*

LOCATION OF MELANOMA	NUMBER	PER CENT	CASES WITH HISTORY OF PREVIOUS MOLE
Lower extremities	68	37	31
Head	62	33	30
Chest	25	14	15
Upper extremities	24	13	13
Trunk	6	3	3
Total	185	100	92 (50 per cent)

*From Ackerman, L. V Texas State J Med 45: 735-744 1949

Gross Appearance

The gross appearance of malignant melanoma varies widely The typical malignant melanoma is deeply pigmented and ulcerated it often has a halo of pigment spreading in the skin around it (Fig 104) The lesion may be flat or papillary ulcerated black with pigment or colorless. An ulcerating neoplasm



Fig 104—Clinical photograph of a typical elevated black malignant melanoma of the skin of the cheek. (W U neg 52-4098)

on the plantar surface of the foot is almost certainly a malignant melanoma although it may exactly resemble a callus (Figs. 105 and 106) (Decker) The subungual malignant *melanoma is a well recognized type if a pigmented area occurs* beneath the nail, this diagnosis must be considered seriously In time of course, the lesion ulcerates and destroys the digit. Huge metastases may arise from an extremely small primary melanoma no more than a few millimeters in diameter We have seen malignant melanomas resemble a pyogenic granuloma. The so-called "freckle type" malignant melanoma is a rare variant, usually seen on the face and may grow quite slowly for years (Fig 107)

Biopsy

Repeated statements are made that the biopsy of a malignant melanoma causes spread. We have seen cauterization of a malignant melanoma followed by the rapid

Fig 105.—Malignant melanoma of the foot relatively nonpigmented. Such lesions may be treated for long periods of time as a benign process

Fig 106.—Pigmented malignant melanoma of the foot with a halo of melanin pigmentation around the ulcerated lesion



Fig 107.—Clinical photograph of "freckle type" malignant melanoma of the face of over ten years duration. Regional metastases were absent and the patient remains cured after excision. (W U neg 52 1099) (Courtesy Dr Ellis Duncan, Louisville Ky)

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on the plantar surface of the foot is almost certainly a malignant melanoma al though it may exactly resemble a callus (Figs. 105 and 106) (Decker) The subungual malignant melanoma is a well recognized type if a pigmented area occurs beneath the nail this diagnosis must be considered seriously In time, of course the lesion ulcerates and destroys the digit. Huge metastases may arise from an extremely small primary melanoma no more than a few millimeters in diameter We have seen malignant melanomas resemble a pyogenic granuloma. The so-called freckle type" malignant melanoma is a rare variant usually seen on the face, and may grow quite slowly for years (Fig 107)

Biopsy

Repeated statem nts are made that the biopsy of a malignant melanoma causes spread. We have seen cauterization of a malignant melanoma followed by the rapid

Fig 105.—Malignant melanoma of the foot relatively nonpigmented. Such lesions may be treated for long periods of time as a benign process

Fig 106.—Pigmented malignant melanoma of the foot with a halo of melanin pigmentation around the ulcerated lesion



Fig 107.—Clinical photograph of freckle type malignant melanoma of the face of over ten years duration Regional metastases were absent and the patient remains cured after excision (W U neg 52 4099) (Courtesy Dr Ellis Duncan, Louisville, Ky)

appearance of satellite skin nodules but know of no such instance following clean incisional biopsy with a cold knife. Primary radical excision should be done if the lesion is located in an area where no deformity will result However if the lesion is of such a size and in such a location that radical excision implies disfigurement or disability, then careful incisional biopsy is indicated There are numerous lesions which may or may not contain melanin pigment which can be confused clinically with malignant melanoma subepidermal nodular fibrosis, infected hemangioma, seborrheic keratosis, and pigmented basal cell carcinoma Frequently malignant melanomas are not recognized clinically Becker reported 151 cases which were verified microscopically but only 115 were diagnosed clinically Furthermore, he described 169 patients with lesions clinically thought to be malignant melanoma, but only 82 proved to have this lesion.

Microscopic Recognition

The obvious malignant melanoma is easily identified microscopically by junctional activity prominent melanin pigmentation deep invasion of the surrounding tissue and many abnormal mitotic figures. It is the interpretation of borderline lesions which taxes the ability and experience of the pathologist. In order to make a diagnosis of malignant melanoma in an adult the following criteria are helpful There is loss of cohesiveness of the neval cells prominence of their nuclei and nucleoli and a disproportionate increase of the nuclear cytoplasmic ratio. The malignant cells extend throughout the epidermis to its most superficial layer (Figs. 108 and 109) The presence of mitotic figures with such changes is almost certain evidence that the lesion is malignant Abnormal mitotic figures have even more significance. The early malignant melanoma is invariably associated with a dermal infiltrate of chronic inflammatory cells Children rather frequently have pigmented tumors. McWhorter reported 172 149 were pigmented nevi, 7 were blue nevi, 11 juvenile melanomas, and 5 malignant melanomas. There is usually little difficulty in the interpretation of the nevi but the identification of the so-called juvenile melanoma is more difficult. McWhorter divided these lesions into two types those with epithelioid cells and those with spindle cells. The epithelioid variant with typical giant cells can be distinguished from the type of malignant melanoma seen in an adult (Fig 110) There is also a spindle cell variant in which the cells have large nuclei, prominent nucleoli abundant cytoplasm and often mitotic figures (Fig 111) There may be merging of these two types. We do not use the term so-called juvenile melanoma" because the spindle cell variant may be seen in an adult. These lesions have a benign evolution whether they occur in a child or an adult. Malignant melanomas occurring in children have the same microscopic pattern as in adults. In the 5 reported by McWhorter 4 died.

Junctional activity is seen associated with the majority of early malignant melanomas. We have seen only one malignant melanoma unconnected with the overlying epidermis which spread and metastasized in a conventional fashion. Bimes has reported two instances of malignant melanomas arising from an intradermal nevus It has been pointed out by Darier Miescher and Allen that if a malignant melanoma lies entirely within the dermis, in practically all instances it is metastatic. Malignant melanomas are noted for their bizarre clinical course.

Fig. 108.—Photomicrograph of a rather superficial malignant melanoma with the malignant cells extending to all layers of the epidermis. (×350.) (W U neg 56-1135A.)



Fig 109.—Photomicrograph of an early malignant melanoma with prominent nucleoli and mitotic figures. (×460.) (W U neg 49-541.)

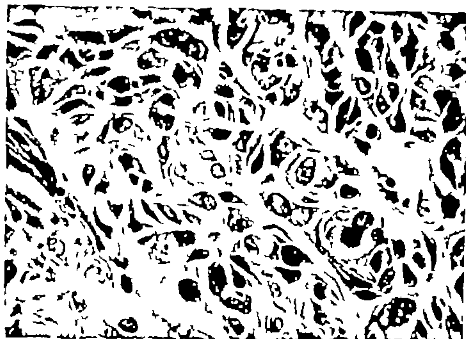


Fig 110 —Photomicrograph of a so-called juvenile melanoma occurring in a child 5 years of age. This is the epithelioid variant with typical giant cells, and can be distinguished from malignant melanoma in an adult. (×600) (W U neg 52-4082)

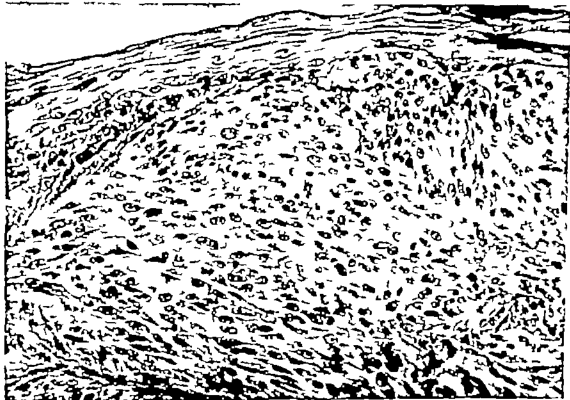
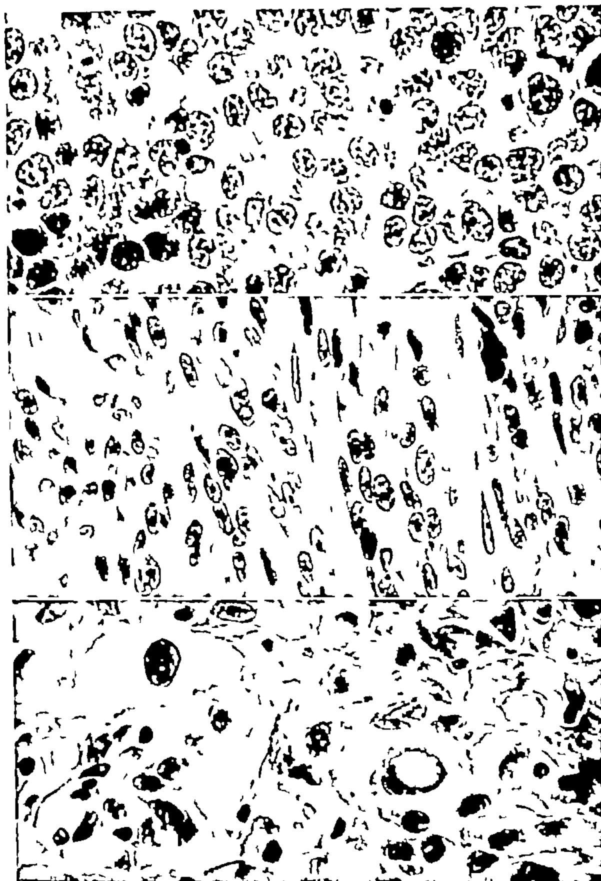


Fig 111 —Photomicrograph of spindle cell variant of nevus excised from skin of abdomen in a child 14 years of age. The cells have a spindle pattern and there are numerous mitotic figures, large nuclei and prominent nucleoli. (×300) (W U neg 58-125)



Figs 112, 113 and 114.—Three photomicrographs of different malignant melanomas at the same magnification demonstrating the possible microscopic variations.

Fig 112.—This tumor resembles a lymphosarcoma. (High power.)

Fig 113.—The spindlelike cells of this tumor resemble those of a fibrosarcoma. (High power.)

Fig 114. The great variation of the tumor cells and the giant forms suggest a liposarcoma. (High power.)

Sections may be presented to a pathologist which show an unusual nonpigmented malignant tumor The pathologist must keep constantly running through his mind a record which repeats "Could this peculiar malignant tumor possibly be a malig nant melanoma?" The pattern of this tumor can resemble a lymphosarcoma, a fibrosarcoma, or an epidermoid carcinoma (Figs. 112 113, and 114) A recent case illustrates this point A young girl 17 years of age presented with a tumor of the scalp which had destroyed underlying bone. Sections were made, and var ious pathologists made diagnoses of osteogenic sarcoma reticulum cell sarcoma, and Hodgkin's disease but none considered malignant melanoma (Fig 115) Complete physical examination of this patient demonstrated a 1 cm. slightly ul cerated primary lesion on the posterior chest wall (Fig 116)

Fitzpatrick studied the activity of the enzyme tyrosinase in malignant mel anoma and benign nevi and stated

> Localization of active tyrosinase in isolated melanoma cells and absence of tyrosinase in isolated nevus cells with the autoradiographic method indicates that melanoma tyrosinase is more active in tyrosine in corporation than tyrosinase in nevus cells.

Spread

Malignant melanoma has been called the black death because of the appalling speed of its metastases and because it grows readily and luxuriantly in almost any organ It spreads quickly by the lymphatics to regional lymph nodes and through the blood stream. The liver lungs, and brain are commonly involved At autopsy one half the patients have metastases to the heart. Occasionally osteolytic metas tases occur within bone. On several occasions material submitted has been from a metastasis. The primary tumor has been small not detectable or previously re-moved. Usually the metastasis occurs in a lymph node. The first manifestation even may be intestinal obstruction due to metastases in the small bowel.

Clinicopathologic Correlation

The treatment of malignant melanoma is wide excision of the primary lesion and radical dissection of the predictable regional lymph node zones. A lesion of the cheek should be treated by excision with skin graft and radical neck dissection. However a malignant melanoma in the midposterior chest should be only widely excised since the sites of its metastases are unpredictable unless already clinically evident. The best prognosis is given to those patients having radical excision of the primary lesion with radical node dissection. The head and neck area is favor able because lesions are often recognized early and because a radical neck dis section is technically a satisfactory method of removing regional nodes. Con versely lesions in the region of the foot often are not recognized until they are advanced, and dissection of the regional lymph node area is anatomically a poor procedure. Pack and his group have advocated en bloc excision of the primary lesion and the draining lymph node area, a procedure based on sound surgical principles. This method of attack is feasible, however only when the tumor and the draining lymph node areas are in fairly close proximity It is impractical for a lesion on the toe when dissection in continuity with the inguinal lymph node area

Fig 115.—Photomicrograph of an undifferentiated nonpigmented malignant melanoma metastatic to the scalp in a girl 17 years of age. (High power.)

Fig 116.—The primary tumor contained areas similar to those in Fig 115. Its true character is indicated by the nevoid pattern seen in this section taken near the surface.

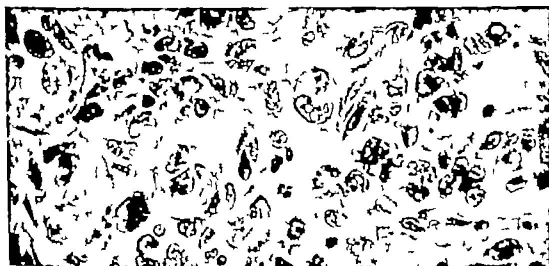


Fig 117.—Photomicrograph of a heavily irradiated malignant melanoma. Note absence of any detectable irradiation effect. (High power.)

is indicated. Moreover from the standpoint of the pathologist, it does not seem worth while to recommend hemipelvectomy for a patient with a malignant melanoma of the foot with involved inguinal lymph nodes. This procedure is recommended in order to increase the radicalness of the operation and to obtain lymph node groups which are not included in the usual radical inguinal dissection. If these intervening nodes prove to be involved then it is not logical to believe that the disease is localized at that point. Furthermore, if the nodes are not involved, the procedure is too radical. Booher reported 13 patients having hip joint disarticulation for involved inguinal and iliac lymph nodes only 1 patient was living without disease Previous inadequate treatment impairs chance of cure. The microscopic pattern of the tumor and the degree of pigmentation apparently does not influence prognosis The five year survival of properly treated patients is between 25 and 35 per cent. It must be remembered however, that recurrence is possible ten to fifteen years after treatment. This lesion is invariably radioresistant (Fig 117) Small lesions under 2 cm and superficial lesions have the best prognosis (Lund Lane)

If prophylactic or therapeutic node dissection is done the rewards are meager Of 46 patients having therapeutic inguinal lymph node dissection, only 5 are alive and well after five years (Booher) Johnson reported 65 malignant melanomas of the skin 33 were treated by local excision, and 32 by local excision and lymph node dissection None of these patients had enlarged regional lymph nodes preoperatively No significant benefit could be demonstrated for prophylactic node dissection

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WOUND HEALING

Harvey R. Butcher, Jr., M.D.

PHYSIOLOGY OF WOUND HEALING

Catabolic Phase

The interrelated growth and maturation of blood vessels, epithelium, and fibrous tissue heal wounds in man by formation of a scar. The regenerative processes that produce the required scar consist of endothelial proliferation, fibroplasia, and epithelization.

The new growth of capillaries and small blood vessels at the wound margin is essential for subsequent healing. Such vascular regeneration (granulation tissue) can be seen grossly in an open wound about the fourth postwound day. This process appears microscopically as early as the third day. It is accompanied by the appearance of fibroblasts and the onset of fibroplasia. New capillaries and fibroblasts also are evident in a sutured wound by the third or fourth postinjury day, at which time invasion of the coagulum between approximated cut edges of the wound begins. Healing of both open and sutured wounds is initiated by early ingrowth of capillaries and fibroblasts if the wound is free of factors delaying wound healing.

Prior to the fourth or fifth day after injury, physiologic processes functioning in the wound remove necrotic tissue, old blood, and bacteria. The surrounding edema fluid contains leukocytes, histiocytes, and a relatively high content of tissue globulin. These elements remove the damaged tissue and eventually remove the fibrin of the wound coagulum before onset of fibroplasia. During this catabolic phase the hexosamine concentration and the degree of metachromasia in the wound

are high (Dunphy) (Fig 118) Increased hexosamine concentration a chromasia are thought to indicate a higher content of mucopolysacch wound tissue than in normal tissue However Grillo found the concent hexosamine in wounds during the first two days after injury to approxim in the serum and interpreted it to be a part of the wound exudate which as the exudate was removed Polysaccharide protein complexes ar sential part of ground substance and are probably a necessary precurso lagen The appearance of an increased concentration of them in woun second and third days suggests that the so-called lag phase (cataboli might well be considered a substrate phase in which the requisite prec collagen appear in wounds (Dunphy)

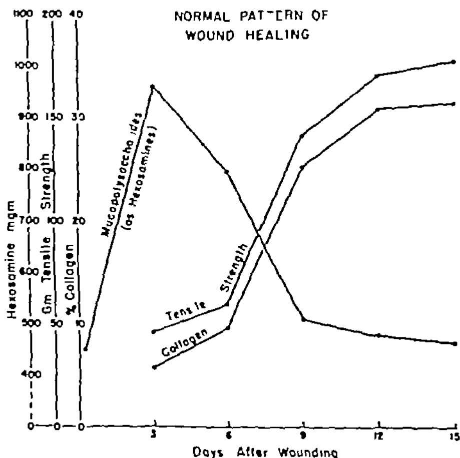


Fig 118.—Normal pattern of wound healing in the white rat. (From Dunphy
Udupa, K. N New England J Med. 253 850 1955)

Anabolic Phase

The appearance of capillary growth and fibroplasia on the third or f after wounding is associated with a decline in hexosamine content of th by the fifth or sixth day a decrease in wound metachromasia is evide reticulin content of the wound (indicated by silver stain impregnation from the fourth to the sixth day then rapidly declines as collagen bundl and wound strength begins to rise In other words from the third or the ninth or tenth day following wounding, a progressive increase in co

content and tensile strength of the wound is associated with decline in wound concentrations of mucopolysaccharides and reticulin The appearance of granulation tissue in the open granulating wound on the fourth or fifth day is associated with the onset of wound contracture (Fig 119) Contracture in open experimental rabbit wounds proceeds exponentially from the sixth to the forty fifth post wound day (Billingham) The strength of the sutured wound rapidly rises during the seventh to ninth days of fibroplasia and reaches a relative plateau but continues to increase at a much slower rate during the period of cicatricial differentiation until the strength of the scar reaches that of the normal surrounding tissue

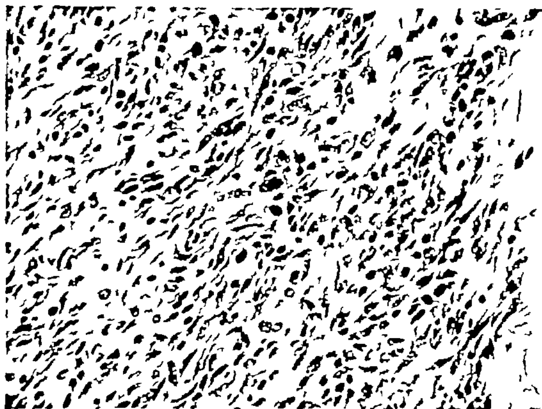


Fig 119 —Photomicrograph showing numerous young fibroblasts in the granulation tissue of early wound healing (W U neg. 58-?719A.)

(Howes) As judged by the rate of increase in wound strength collagen deposition occurs at the same rate in such diversified tissues as muscle, fat, and fascia. Of course, all of these heal by the same basic mechanism. Wound strength also increases at the same rate in laboratory animals as in man The same rate exists for wound healing in the mouse as in man despite a much higher metabolic rate in the mouse. Similarly the strength of wound fibroplasia two weeks after injury is the same per unit area of wound in different tissues and different laboratory animals (Howes)

The anabolic phase of wound healing (from the fifth to the fourteenth or fifteenth postwound day) is accompanied by a *gradual decline in the number of capillaries* in the wound as more and more collagen is deposited. The reduction in vascularity continues until cicatricial differentiation is complete.

Healing by epithelization is particularly important in open wounds. Altl wound area is reduced primarily by contracture healing is not completed wi epithelial growth. After the appearance of granulation tissues in the floor open wound the vertical edges of the wound become flat and resurfacing beg epithelial migration. By the eighth or ninth day a distinct border of new e lium is seen along the edges of uncomplicated granulating wounds. Epi ingrowth combined with contracture completes healing. Epithelization as a m of healing is more important over bony areas such as the scalp or patella wound contracture is limited.

Differentiation of Cicatricial Tissue

Two to three weeks after a wound has been closed the deposition of co is maximal. Subsequently excess collagen is slowly absorbed as the scar ma The differentiation and partial resorption of collagen takes six months to a the time required for this process is effected by the rate of functional recov the part. Such absorption and differentiation do not occur if function has grossly impaired. Infection complicating wound healing may result in a mass of scar tissue which prevents return of function of the part. In such ins the bulk of undifferentiated scar tissue will remain and loss of the functio continue if surgical repair is not performed. Such inability to regain joint fu following the deposition of massive scars associated with burns of the axilla or antecubital spaces is a factor in the failure of these scars to decrease in Maturing collagen bundles in soft tissue scars become aligned along lines c sion. For this reason vertical abdominal scars are likely to be broader than verse ones. The lines of tension (Krisel's lines) tend to be transverse to the tion of the underlying muscle pull. Incisions in skin parallel to tension lines in narrower and less disfiguring scars (Harkins).

The differentiation of connective tissue is a protracted and variable pi its variability depends upon the tissue wounded and to some extent upon the tion of the cicatrix. The healing of cartilage and bone is accompanied l deposition of calcium salts and the appearance of cartilaginous cells as soon initial connective tissue is laid down. If cartilage is being repaired the appe of cartilage cells ends the process of healing save for slow increase in the the collagenous fibers and their orientation along directions of stress. If b being regenerated undifferentiated ossification occurs and cartilage cells disa Later the primary callus is differentiated and cortical bone forms with the a tion of great masses of primary callus. Considerable stress has been placed function of the osteoclast in the realignment of the callus along lines of However their importance is at least partially discounted by the fact that t sociated connective tissue develops heavy collagenous fibers parallel to the of stress. The reorientation of the connective tissues in healing bone is un ated with any known special cell activity (Howes).

A 2 week-old scar is red because of abundant capillaries thereafter th becomes white as the young collagen slowly differentiates and the numl capillaries decreases. Disappearance of blood vessels associated with thicl

of collagenous bundles is one of the reasons why granulations 2 months or more old do not accept skin grafts as well as freshly formed granulations. The lessened vascularity of long standing granulating wounds is associated with the age of the underlying cicatrix.



Fig 120—Photograph of a long standing chronic stasis ulcer showing unhealthy sparse granulation tissue in dense scar. This patient had had stasis ulcers in the area for twenty-two years. The arterial circulation was normal in the extremity (W U neg 57 5075)

Long-standing ulceration of the leg is associated with such dense subcutaneous and fascial scarring that the granulations appear sparse and irregularly distributed (Fig 120) Even less granulation tissue may be present if arterial blood flow to the area is deficient (Fig 121)

The growth of granulations upon an open wound surface is requisite for epithelization. However epithelization will not occur over granulations that are

depressed or protuberant The spread of epithelial cells across granulations of just the right height and cleanliness stops further capillary growth The reasons are unknown (Howes)



Fig 121 —The extremity shown was the site of stasis ulcer for fifteen years By the time of this photograph however extensive femoral occlusive disease had supervened The ulcers contained little healthy granulation tissue. This finding suggests arterial flow deficiency in any ulcer if invasive infection is absent. (W U neg 57-6936)

GENERAL FACTORS AFFECTING WOUND HEALING

Dehydration anemia, starvation with severe protein depletion scurvy, previous wounds, age, and hormones have been considered as general factors which influence the healing of a wound The adverse effects of many of these factors on wound healing have not been proved in man and their experimental investigation has resulted in controversial conclusions.

Dehydration, Anemia, and Protein Depletion

Sandblom reported the deleterious effect of dehydration on healing of excisional wounds in rabbits and a lessening of tensile strength of 5-day-old rabbit skin incisions after acute anemia had been produced without hypoproteinemia however Levenson found anemia had no effect upon healing of a standard open wound in rats The rats he studied were fed an iron-deficient milk diet until an anemia of about 6 Gm. per cent hemoglobin was produced. He also measured the tensile strength of the wounds on the fifth postincision day The healing of experimental burns has not been altered by nonprotein diet or anemia in the burned rat (Andrews) As far as dehydration alone is concerned, Byrd showed that the tensile strength of stomach incisions was reduced in dehydrated animals However he found a reduced strength of the entire stomach wall in dehydrated control animals

It is generally believed that patients with poor nutritional status are more likely to have impaired wound healing This is based upon the fact that the highest incidence of wound complications such as dehiscence occurs in elderly cachetic patients with diseases of the gastrointestinal tract. These patients may have a low plasma protein concentration associated with some chronically debilitating disease such as cancer or chronic infection. However single factors such as hypoproteinemia do not alone produce clinical retardation of wound healing Many patients manifesting poor healing have normal serum protein concentrations conversely many patients heal their wounds despite significant degrees of hypoproteinemia. Only if starvation and hypoproteinemia are associated with significant nutritional tissue edema is wound healing likely to be impaired. The healing of granulating wounds such as occur in third degree burns is thought to be impaired in the presence of severe protein deficiency (Levenson) However the possibility of such factors as a high incidence of wound infection in such patients may well be responsible for the delay in healing observed Gottlieb reported that delay in healing and infection were not problems in abdominal incisions of prisoners in war camps despite the presence of marked nutritional deficits In the absence of starvation severe enough to produce diarrhea marked dehydration or gross tissue edema, caloric and protein depletion probably have little effect upon clinical wound healing Sisson found a reduction in the mean tensile strengths of experimental abdominal wounds in the rat associated with starvation sufficient to reduce body weight to 70 per cent of normal

Udupa showed a less rapid rise in hexosamine concentration and in collagen deposition in rats with severe protein deficits than in normal rats (Fig 122) He noted that the addition of methionine alone to the nonprotein rat diet rapidly caused the concentration of these materials to return toward normal. Other workers have shown a difference between the lengths of the lag phase (latent period before beginning gain in tensile strength) of experimental wounds in control and in protein-deficient animals. Despite a longer lag period in protein depleted rats, the rate of increase in tensile strength of the wound was the same as in normal rats (Kobak) There was no correlation between weight loss plasma protein concentration, and tensile strength. Rats with serum proteins as low as 3 2 Gm. per cent

produced wounds with as great a strength as did rats with serum proteins c Gm per cent The lower tensile strength of wounds in protein-deficient rats ing the third and fifth postwound days apparently was due to (a) dimin in the number of fibroblasts decrease in their rate of maturation and a ge failure of the fibers to organize with adequate density along lines of stress delay in maturation of the reticulum into mature collagen Tissue edema wa sent in these animals but wound infection was common The protein-deficien appeared to resist infection poorly Occasionally abscesses were found in s lines and diffuse lymphocytic wound infiltration was common (Kobak)

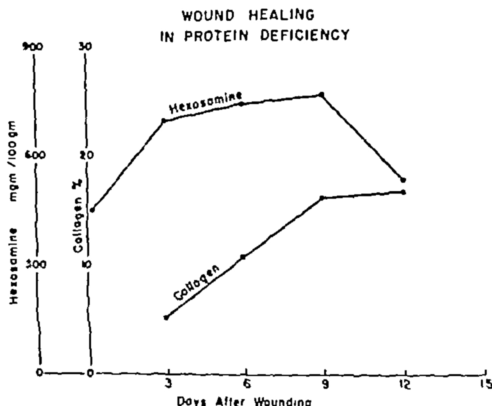


Fig 12 —Pattern of healing in protein-deficient rats. (From Udupa, K. N., Woess F and Dunphy J E. Surg Obst. & Gynec 102: 639 1956)

Ascorbic Acid Deficiency

The inability of the scorbutic sailor to heal wounds made scurvy the nutritional condition known to affect wound healing adversely Wolbach sl that the morphologic consequences of experimental ascorbic acid deficienc practically restricted to the mesenchymal supporting tissues and may be exp as *failure* of formation and maintenance of intracellular materials. The : *mechanism* by which ascorbic acid promotes the formation of collagen i known, however it would appear that the presence of a protein componen a carbohydrate component known to exist in wounds requires the preser ascorbic acid before their union can result in adult collagen (Hunt)

Many workers have studied the histology of wounds in the absence of vi C (Hunt) Cellular proliferation is delayed as well as the formation of p lagen or reticulin maturation of reticulin is absent Once cellular prolife

has started however it continues although maturation of fibroblasts does not occur While the scars of normal animals after fourteen days consist of mature fibrocytes in a matrix of collagen those of deficient animals are composed of fibroblasts in a procollagenous matrix Vascularization does not proceed normally in deficient animals. The resulting scar is puckered discolored hemorrhagic, and indurated. Hunt also noted the reversion of apparently mature collagen to a precollagenous state in the wounds of normal animals placed on a scorbutic diet twenty-one days after wounding This is in keeping with the breakdown of long

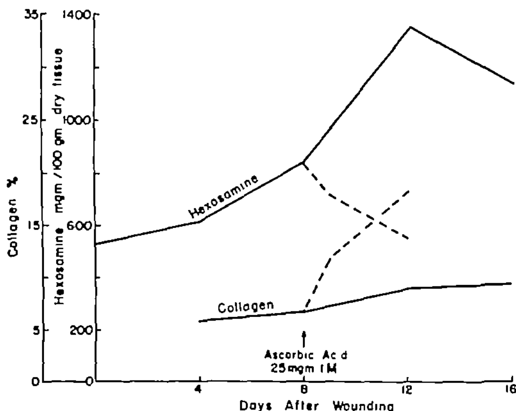


Fig 123 —Pattern of wound healing in scorbutic guinea pigs The dotted lines indicate the change in this pattern which followed the intramuscular injection of 25 mg of vitamin C daily (From Dunphy J E., Udupa, K. N and Edwards L. C Ann. Surg 144: 311 1956.)

healed wounds in scorbutic men observed in the past Wound healing in normal human beings subjected to controlled vitamin C deficiency has been observed by Crandon and Lund. Forty two days after the beginning of the experimental diet the plasma vitamin C level reached zero but the white blood cell ascorbic acid did not reach this level for 122 days. An experimental wound 2 inches in length made three months after the start of the diet healed normally in so far as gross and histologic appearances were concerned however after 161 days a few petechiae were noted on the limbs and a second wound made six months after beginning the vitamin C-deficient diet showed grossly faulty healing The wound edges failed to unite below the skin There was no formation of collagen, and vascular elements

were absent by histologic examination of the 10 day-old biopsy specimen Following this biopsy, the patient was given 1 Gm. of ascorbic acid daily Ten days later another wound biopsy contained ample intracellular substance and capillary formation

Dunphy showed that scorbutic guinea pig wounds were not deficient in ground substance mucopolysaccharide as measured by hexosamine concentration However the wound hexosamine concentration remained high and was associated with a continued low concentration of mature collagen in the ascorbic acid deficient guinea pigs. A rapid reversal of this situation followed the introduction of ascorbic acid to the diet of the ascorbic animals on the eighth postwound day (Fig 123)

Age

It is well recognized clinically that similar wounds heal faster in the young than in the old DuNouy first showed this to be true for open wounds Howes and Harvey found the lag phase of wound healing to be shorter in the young experimental animal than in the old However, actual rate of increase in tensile strength was no greater in the young than in the adults the slopes of their time-tensile strength curves were parallel during the fourth to the sixth day The period of increasing fibroplasia began sooner and lasted longer in the young than in the adult animals lasting from the third to the seventh day in the young and from the fourth to the sixth postwound day in the older group Although studies indicate a definite effect of age upon wound healing in experimental animals, the specific influential factors involved are not known. This effect may be caused by a decline in vascularity associated with increasing age of the area being studied.

Previous Injury

The effect of a previous injury upon wound healing in the rabbit has been studied by Sandblom. He found by tensile strength measurements that a second experimental wound healed more rapidly than the first if the second wound was made six to forty days after the initial one. The rates of gain in tensile strength were similar after the fifth or sixth day but the secondary wounds were stronger at any specific postwound time The healing strengths of secondary wounds exceeded that of the primary wound through the first ten days of healing Sandblom noted that secondary wounds were stronger as early as the first or second postwound day (The differences in his plotted data for this early postwound period appear to be small, and probably are significant only after 4½ or 5 days)

Billingham reported no effect of a healing primary wound in remote locations upon the rate of contracture of secondary wounds He found a linear relationship between the log of the remaining square centimeters of area of a wound and the days after wounding from the fifth or sixth to approximately the fortieth postwound day This linear relationship was unaltered by prior wounding These experimental findings lead to conclusions which differ from those of Sandblom. Clinical impressions suggesting increased rate of healing of second wounds are based primarily upon secondary wounding in the same area. This is exemplified by abdominal wounds which have been reopened seven to fifteen days after an

initial operation. An increased rate of healing is possibly observable in such re opened wounds only in the absence of infection, hematoma, or other local factors which may deter healing

Hormones

The knowledge concerning hormonal influences upon connective tissue and wound healing is limited (Asboe Hansen)

Howes has shown that the dose of cortisone given parenterally crucially af fects the time that granulations appear in open rabbit wounds. Large parenteral doses repressed their appearance while smaller doses did not Even a small amount of cortisone applied locally to the open wound delayed the appearance of granula tions. Microscopic sections of the wounds treated with cortisone showed that the blood vessels did not develop fibroblasts did not proliferate and reticulin was not deposited However large doses of cortisone only delayed the appearance of granulation tissue in the wounds for approximately eighteen days Following this delay they appeared and grew In other words cortisone did not completely suppress fibroplasia but only delayed it. The amount of cortisone required experi mentally to produce significant gross changes in wound healing was greater than the usual clinical dose. Wound healing is not grossly impaired by 2 mg per kilogram of cortisone daily (Cole) The ability of locally applied cortisone to in hibit the formation of granulation tissues probably explains its clinical usefulness in *patients undergoing operations upon joints.*

Other as yet undefined, physiologic factors probably influence wound healing The wound of a debilitated postoperative patient with irreparable disease may heal but little during the two to three weeks prior to death (Fig 124) The factors responsible are obscure.

LOCAL FACTORS AFFECTING WOUND HEALING

Infection hematomas excessive amounts of crushed or necrotic tissue foreign bodies, and poor local blood flow all delay wound healing Early invasive or necrotizing infection is the most common cause of delayed fibroplasia The presence of hematoma, foreign bodies, or sloughing tissue will by themselves retard the onset of healing but an important practical effect is their enhancement of bacterial growth. Once wound infection becomes chronic with formation of an abscess or sinus, fibroplasia at the periphery may produce excessive scar Capillaries do not extend into areas of undrained pus or sloughing tissue Surgeons may avoid many wound infections by observing all rules of asepsis and by use of the delayed closure of grossly contaminated wounds. Hematoma is prevented by careful ligation of the smaller vessels in the wound and by transfixion of all major blood vessels with nonabsorbable sutures Serum collections beneath skin flaps and in areas of potential dead space can be minimized by the obliteration of dead space and by immobilization of the part. The surgeon must avoid excessive tissue trauma such as occurs with mass ligation of tissues the use of steaming hot moist sponges and forceful retraction in an attempt to gain exposure through an inade quate incision. Before closure, all small clots and loose fat should be washed from the wound.



Fig 124 —Photomicrographs of a 16-day-old cutaneous incision in a 43-year-old patient dying of carcinoma of the bladder Note the lack of fibroplasia and collagen. (W U neg 58-2718A.)

Foreign bodies interfere with wound healing by causing inflammation of adjacent tissue and by harboring bacteria which result in abscess and sinus formation. In the past talc granuloma was a special type of foreign body reaction which developed in wounds and in abdominal cavities soiled by talc from sterile rubber gloves. Severe chronic inflammation and excessive fibroplasia develop about the doubly *refractile particles of talc (see Fig 937 p 873) Although talc is no* longer used to powder rubber gloves patients occasionally are seen with intestinal obstruction, fistulas, and chronic sinus tracts caused by talc introduced years before. Powder developed from cornstarch is now used in most hospitals. This material is much less nocuous than talc but causes some tissue reaction All powder should be washed thoroughly from the outer surface of surgical gloves before an operation.

Wound sinuses persist because of (1) inadequately drained abscess (2) foreign body (3) some chronic granulomatous process such as tuberculosis regional ileitis or actinomycosis, and (4) the presence of neoplasm. These factors also may play a part in the maintenance of a fistula between the skin and the gastrointestinal tract biliary tract or urinary tract however fistulas most often persist because of partial or complete obstruction of the tubular tract beyond the fistula. For example the patient with a permanent cecocutaneous fistula following appendectomy for acute appendicitis may have any of the five factors just discussed as its cause. If all of them are absent, the fistula will close spontaneously If the appendix has been ruptured a fecolith near the appendiceal stump may be the cause of a persistent sinus or fistula. Older persons may have unrecognized carcinoma of the cecum or a partially obstructing lesion of the sigmoid colon which prevents spontaneous closure of the fistula.

The persistence of a sinus draining from a wound most often is caused by nonabsorbable suture material The relationship of suture material to wound infection deserves some comment. Silk or cotton sutures reside in the clean wound permanently (Fig 125) however if such a wound becomes infected the sutures likely will be extruded intermittently through sinus tracts for many months The use of catgut in such circumstances is not followed by such persistent sinuses because the catgut is absorbed by an accompanying local tissue reaction which is histologically more severe than that occurring about silk. If a wound closed with catgut becomes infected in the first few days it is more likely to disrupt than if closed with nonabsorbable suture material This is particularly true of hernia repairs. Nearly all catgut herniorrhaphies which become infected recur The incidence of recurrence after infection is less when silk is used despite "silkosis"

All factors which increase the amount of wound exudation have a delaying effect on wound healing Obviously then the amount of suture material used is important. Practically a sufficient amount of suture material must be introduced to insure accurate wound approximation without undue tension. Catgut, particularly the nonchromicized variety produces a greater degree of wound exudation and more delay in healing than does less reactive nonabsorbable sutures such as silk, cotton nylon or steel wire. Stainless steel or tantalum wires produce less reaction than silk or cotton All nonabsorbable sutures maintain the integrity of infected wounds much better than catgut. Wire does this as well if not better

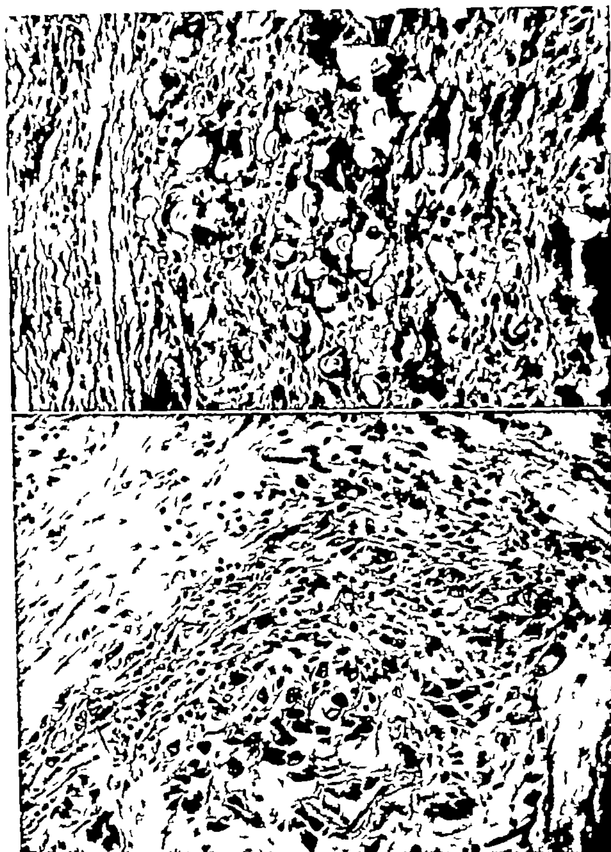


Fig 125 —Photomicrographs of tissue reactions to cotton sutures (above) and to silk sutures (below) after being in place for three months and two years respectively (W U negs 58-4081 and 58-4087)

than silk and is less likely to be extruded from the wound The effects of different techniques of wound suture upon wound strength have been studied in the rabbit by Sandblom. The tensile strengths of cutaneous wounds closed with 000 black silk by various techniques were measured five days after suture. In the wounds closed without tension he found no difference between the healing strength of wounds closed with interrupted suture and wounds closed with a continuous suture, nor was healing affected by different suture spacings or by the use of plain or toothed tissue forceps while introducing the sutures however, he did show that the strengths of wounds closed under tension were less than those closed without tension.



Fig. 126.—Mal perforans pedis is shown in a typical plantar location. The patient was diabetic. Pedal pulses were normal but neuropathy existed. (W U neg 57-5286)

The blood supply and temperature of the area wounded have important influences upon the rate of healing For example, the skin temperature in the feet is several degrees less than that of the abdomen or trunk despite the fact that roughly the same cutaneous vascularity exists in the two regions. Clinically wounds of the abdomen heal significantly more rapidly than do those of the foot or distal extremity Sutures in clean incisions about the foot often need be left in place twelve to fourteen days while the sutures in an abdominal incision can be removed safely after six or seven days Although cutaneous temperatures of the abdomen and chest approximate those of the head and neck the increased blood flow through the skin about the face allows the removal of sutures in this area after three or four days without danger of wound dehiscence. Richer blood supply also accounts for the less frequent occurrence of infection in head and neck

wounds than in wounds of the trunk. The effect of poor blood supply upon healing is evident clinically in irradiated tissue wounds. Prior irradiation appears to be deleterious because of decreased vascularity accompanying the irradiation scarring. The inability to secure good wound healing in extensively irradiated areas is one factor which makes the operative treatment of postirradiation persistent neoplasm so difficult. The adverse effect of irradiation upon wound healing has been studied experimentally by Nickson.

Mal perforans pedis occurring in patients with diabetes and peripheral diabetic neuropathy represents a special type of wound which fails to heal because of continued trauma. It is associated with loss of sensation in the skin overlying areas of pressure. These deep undermining chronic ulcers of the plantar skin occur typically over the heads of the metatarsals. Because of the absence of sensation persistent pressure in the area is thought to impair the cutaneous blood supply sufficiently to cause keratotic calluses which easily become infected and ulcerate (Fig. 126). Many of these patients have good peripheral arterial blood flow. Microscopically the vessels in the plantar skin about the ulcer may show little evidence of obliterative disease. The neuropathic deficit in skin sensation allows large ulcers to exist with little or no pain.

WOUND HEALING IN SPECIAL TISSUES

Although wound healing in the gastrointestinal, urinary and biliary tracts is physiologically similar to soft tissue wounds, the nature and special functions of their linings require special suture techniques in order to avoid ulceration or disruption of suture lines in them. In the serosally covered gastrointestinal tract optimum healing of suture lines follows accurate serosal approximation. A mucosal row of sutures in the gastrointestinal tract accurately approximates the mucosa and aids hemostasis. The larger submucosal vessels should be separately clamped and ligated. The suture material used in the gastrointestinal tract varies in many institutions. We believe chromicized catgut is best used for mucosal suture because of the time often required for nonabsorbable sutures to eventually slough from the mucosal surface into the lumen. Years may pass before this is accomplished if the sutures have not been tied tightly enough to strangulate the tissue within them and allow their early passage in the fecal stream. Interrupted silk sutures in the mucosal surface of the colonic anastomoses may persist and be associated with granulomatous reactions in the bowel wall which are mistaken for suture line recurrence (Figs. 127 and 128). Nonabsorbable sutures should be avoided when suturing the mucosal surface of the stomach. Persistent silk sutures in gastric mucosal surfaces may lead to chronic peptic ulceration. Disappearance of absorbable sutures from the mucosal surface of the stomach is rapid and complete (Fig. 129).

Healing of suture lines in the biliary and urinary tract is best obtained by careful mucosal approximation with interrupted absorbable sutures. Silk or other nonabsorbable material probably should not be used to ligate the stump of the cystic duct or to close the common bile duct, or in suture lines of the urinary tract. In these sites, the suture may pass into the lumen and become a nidus

for the formation of calculi. Accurate mucosal approximation in both the biliary and urinary drainage systems is mandatory to avoid stricture at suture lines. This fact has been particularly stressed by Lahey in the treatment of the biliary tract stricture. The mucosal suture of the ureters to the colon has proved the most efficacious method of ureteral sigmoidostomy (Cordonnier) The accurate approximation of the ureteral and colonic mucosal surfaces minimizes the amount of surrounding contracting collagen and avoids hydronephrosis and pyelonephritis (Fig 130) *The careful approximation of the respective mucosas in suture of* ureter to intestine, either colon or ileum prevents excessive fibrosis (Fig 131) (Bricker)

Most surgeons believe that the construction of an ileostomy or permanent colostomy is best obtained by careful approximation of mucosa to skin with inter



Fig 127 Photograph shows a barium enema made four months after resection of the sigmoid colon for carcinoma The area of irregularity and partial stenosis is at the suture line. Interrupted silk sutures had been used in the inner as well as the outer layer of the anastomosis The roentgenographic diagnosis was suture-line recurrence of carcinoma how ever sigmoidoscopic examination showed multiple silk sutures in the a of reaction Biopsies showed chronic inflammation. (W U neg 58-2246.)

Fig 128 —Photograph of barium enema showing the same su strated in Fig 127 two and one-half years after operation Although the ar and the degree of stenosis had lessened the suture line is still evident. Sigm mination at this time still showed silk suture material anastomosis. A resecte specimen associated with recurrence of the er showed peri hroni inflammation in the suture-line scar No c ent in it. (W)

rupted suture material Such mucosa to skin approximation allows healing per primum which is unlikely to be followed by stomal stricture

The transplantation of tissues and the fate of these grafts may be considered a part of the healing process The use of bone, cornea, cartilage, and skin from tissue banks has proved useful In all of these instances however, the grafting procedure is homologous and the grafts are dead The only autogenous graft commonly used is of skin This is living and stays alive Of course, autogenous parathyroid tissue and thyroid tissue have been successfully transplanted and have continued to grow and function however any tissue, be it autogenous or homologous to which the blood supply has been interrupted for a significant time



Fig 129—Photograph of a 3-week-old experimental gastric suture line. The canine stomach was transected and continuity re-established with two layers of interrupted silk sutures along one half the circumference the other half was closed with serosally placed interrupted silk and a mucosal layer of interrupted chromicized catgut of the same caliber The catgut disappeared but the silk persisted. (W U neg 58-5895)

must be considered dead All dead tissue transplants including homologous fascia, bone and cartilage are slowly replaced by host tissue (creeping substitution) Whether the new structure continues to persist in outline depends upon its function. A piece of tendon placed in the liver will gradually be absorbed only a scar remains However if tendon is used between the ends of a cut tendon it persists and takes on the appearance of the adjacent tendon (Howes)

The use of homografts to replace occluded and aneurysmal major arteries has been undertaken extensively during the past fifteen years with fair clinical results. Some of these grafts are slowly invaded by host fibroplasia as the micro-



Fig 130 —*Above* Intravenous pyelogram of a 21 year-old woman who had undergone ureterosigmoid anastomosis by the Coffey I technique *seventeen years before. She now* sought medical therapy because of episodes of pyelonephritis and a large left abdominal mass This mass proved to be a markedly hydronephrotic nonfunctioning left kidney (W U neg 57 7254)

Below Gross specimen removed from the same patient The right ureteral orifice (on the left) was polypoid, fibrotic, and chronically inflamed. The left orifice (on the right) was the site of a transitional cell carcinoma limited to the intramural ureter and the colonic wall (W U neg. 57 7058)

scopic structure of the graft slowly disintegrates (See Vessels, p 893) The fibrinous coat lining the arterial graft soon after its insertion is slowly replaced by fibrous tissue and a pseudoendothelial surface, while collagenous encasement takes place on the adventitial side of the graft A similar encasement of arterial synthetic prostheses by collagenous tissue takes place after their implantation



Fig 131 —Photomicrograph showing a healed mucosa to-mucosa ureterointestinal anastomosis Cicatricial formation is minimal. (W U neg 58-4207)

ABNORMAL WOUND HEALING

The commonest form of abnormal wound healing is the formation of keloid. Keloid may be considered a hypermaturation and excessive deposition of collagenous tissue The collagenous bundles formed are very large and associated with very few fibrocytes (Fig 132) The prevention of keloid formation is at times quite difficult particularly in people who are unusually prone to form them (see Fig 59) They occur most commonly in the Negro Simple excision of a keloid with accurate wound approximation may prevent re formation of the keloid X ray therapy occasionally is used after keloid excision in the hope of preventing its recurrence.

Metastatic calcification in clean surgical wounds occurs rarely It is likely that many wounds in which calcification with bone formation has occurred have

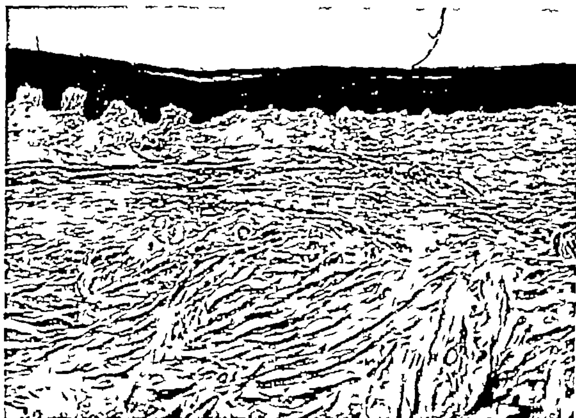


Fig 132.—Photomicrograph showing very large hypermature collagen bundles characteristic of keloids. (W U neg 58-2301)

been associated with hematomas. However this does not always appear to be so (Sanders) Tissue calcification occurs rarely in the walls of venous varicosities and in the fibrotic subcutaneous tissues about stasis ulcers. The appearance of calcification in arterial homografts is quite common after long periods of implantation.

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Chapter 3

ORAL CAVITY

INTRODUCTION BIOPSY
SPECIFIC INFECTIONS
CHRONIC NONSPECIFIC INFLAMMATORY PROCESSES
BENIGN TUMORS
- Pyogenic Granuloma and Pregnancy Tumors
- Hemangioma
- Peripheral Giant Cell Tumor
- Rare Tumors

MALIGNANT TUMORS
- Leukoplakia
- Epidermoid Carcinoma in Situ; Multiple Foci of Origin
- Verrucous Carcinoma
- Epidermoid Carcinoma
- Lymphosarcoma
- Lymphoepithelioma

INTRODUCTION BIOPSY

Dentists have the best chance of seeing a high percentage of the early lesions of the oral cavity It is their responsibility to examine the oral cavity carefully for evidence of systemic disease, precancerous lesions and tumors Patients with a suspicious lesion should be referred for proper study and biopsy Lesions within the oral cavity are often poorly biopsied An adequate biopsy may be difficult to obtain from certain intraoral lesions such as deep-lying tumors at the base of the tongue. It is imperative that a deep biopsy be taken rather than a small super ficial one.

SPECIFIC INFECTIONS

Tuberculosis is a rare lesion within the oral cavity It is usually seen on the tongue as a painful ulcer but it also may occur on the buccal mucosa (Oppen heim) It is associated with pulmonary tuberculosis in about 100 per cent of instances. Microscopically there are typical tubercles with acid fast organisms.

Syphilis may produce a gumma in the tongue or palate which may not be painful but forms an indurated mass. This lesion must always be biopsied even though the serology is positive, because about 25 per cent of patients with cancer of the tongue have associated syphilis. This gummatous lesion is a granulomatous process with giant cells. Weed has reported several instances of ulcerative disease of the mouth and pharynx due to histoplasmosis.

CHRONIC NONSPECIFIC INFLAMMATORY PROCESSES

There are numerous low grade inflammatory lesions in the oral cavity produced by ill fitting dentures ragged sharp teeth and poor dental hygiene (Fig 133) Localized overgrowth of the epithelium with or without ulceration is common, and it is not rare to see large pseudotumors made up of fibrous tissue and chronic inflammatory cells Large masses of plasma cells associated with chronic inflammation within the oral cavity are also common (Figs 134 and 135) Removal of the offending agent allows the pathologic process to subside The only danger to the patient is the tendency for the pathologist to diagnose the lesions incorrectly because of aberrations in the overlying epithelium The inflammation distorts the epithelial pegs and may produce areas in which squamous cells are isolated from



Fig. 133 —Localized overgrowth of the upper alveolus produced by an ill fitting denture (W U neg 52-4100) (Courtesy Dr C. A Waldron St Louis Mo)

the overlying epithelium (Fig 136) If the pathologist pays attention to the inflammatory process and notes that the squamous cells are well differentiated and that inflammatory cells may be present between them, he will diagnose the lesion correctly A chronic nonspecific inflammatory process rarely may produce sufficient epithelial distortion to cause a diagnosis of cancer even by the experienced pathologist We have seen four cases exhibiting marked epithelial abnormalities and destruction of the mandible which were treated by irradiation and/or radical resection and neck dissection Needless to say the lymph nodes contained no tumor

BENIGN TUMORS

Pyogenic Granuloma and Pregnancy Tumors

Pyogenic granuloma is an exaggerated response to minor trauma. It appears in the oral cavity as an elevated dark red lesion which may or may not be

ulcerated (Fig 137) Large masses of proliferating endothelial cells are separated by inflammatory cells. Characteristically the covering epithelium almost meets at the base of the lesion (Fig 138) It heals as a residual fibrous mass or fibroepithelial papilloma (Kerr) An identical lesion occurring during pregnancy is often incorrectly diagnosed as an infected hemangioma.



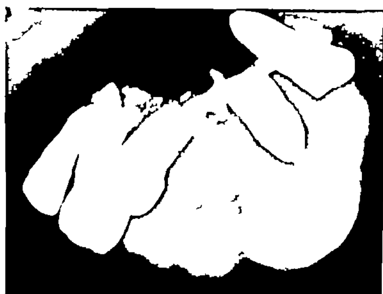


Fig 134 —Gross photograph of a resected pseudotumor of the alveolar process made up of fibrous tissue and chronic inflammatory cells. (W U neg 52 3842)

Fig 135 —Roentgenogram of the alveolar process from which the pseudotumor shown in Fig. 134 was resected, showing the extent of the soft tissue mass

Hemangioma

Hemangioma and lymphangioma are vascular malformations which frequently occur on the tongue or gingiva in children or young adults. We have



Fig 136 —Extreme pseudoepitheliomatous hyperplasia of an inflamed gingiva This was incorrectly diagnosed as carcinoma by several experienced pathologists. *Above* (×40) (W U neg. 57-483) *Below* (×115) (W U neg 57-4784)



Fig 157 —Pyogenic granuloma of the buccal mucosa sharply circumscribed and elevated (Contributed by Dr Wilson Burford, Columbia, Mo. EFSCH 15461)



Fig 158 —Typical low power pattern of a pyogenic granuloma. Note the elevation above the lining epithelium and its narrowing at the base. (W U neg 51 1069) (Contributed by Dr Zola Cooper St. Louis, Mo.)

seen such lesions on the tongue form soft cystic masses so large that they interfered with speech and mastication Microscopically they show endothelium lined spaces some of which contain blood Treatment by excision or sodium morrhuate injection depends upon their size and location

Peripheral Giant Cell Tumor

The peripheral giant cell tumor usually occurs in young children but may appear at any age It is more often seen on the lower than upper gingival ridge arising probably from the periosteum A soft to firm mass forms which pushes aside the teeth and may erode the mandible Microscopically it shows numerous giant cells an active vascular stroma and at times small amounts of bone production Whether or not it is a true neoplasm is doubtful since it never metastasizes The treatment is excision or small amounts of protracted irradiation

Rare Tumors

We have seen two neurilemomas involving the tongue and several neurofibromas beneath the epithelium of the pharynx (Slaughter) Mixed tumors are discussed in the chapter on Major and Minor Salivary Glands (p 425)

MALIGNANT TUMORS

Leukoplakia

The most common malignant tumor of the oral cavity is squamous carcinoma. It may arise from pre-existing leukoplakia or follow long-continued irritation from an ill fitting denture or a sharp tooth Leukoplakia is common within the oral cavity is of unknown etiology and occurs most frequently in the buccal gingival gutter It appears as filmy grayish white slightly raised areas A few of the lesions which are diagnosed clinically as leukoplakia probably will progress to cancer leukoplakia is associated with a high percentage of intraoral cancer If the term leukoplakia is limited to lesions showing microscopic changes, consisting of basal cell hyperplasia and focal epithelial atypia then the likelihood of its transition to cancer is greater In any event it seems worth while to excise such areas as a prophylactic procedure

Epidermoid Carcinoma in Situ, Multiple Foci of Origin

Carcinoma of the oral cavity may arise from epidermoid carcinoma in situ (Fig 139) How often this occurs is not known neither is the speed of its evolution We have seen a 60-year-old man with a small slightly elevated pinkish gray area on the floor of the mouth which was excised and found to be epidermoid carcinoma in situ. Three months later invasive carcinoma was present at the site of excision and in the underlying mandible Another patient had epidermoid carcinoma in situ with multiple foci of origin over a wide area of the oral mucosa. This lesion was present for five years before invading carcinoma appeared and caused the death of the patient

Epidermoid carcinoma in situ may also develop on the periphery of an obvious carcinoma Therefore it is necessary to give the invasive carcinoma a wide

margin whether treating by irradiation therapy or surgery. As more and more carcinomas of the oral cavity are cured, it is becoming apparent that the entire oral cavity mucosa is susceptible to the development of carcinoma. If a patient has one carcinoma of the oral cavity the chances of that patient developing another carcinoma is increased. In 206 patients with carcinoma of the oral cavity seen at the Ellis Fischel State Cancer Hospital, there were two cases with two independent carcinomas on admission and eight other instances of second "primary" carcinomas developing after treatment of the initial tumor.

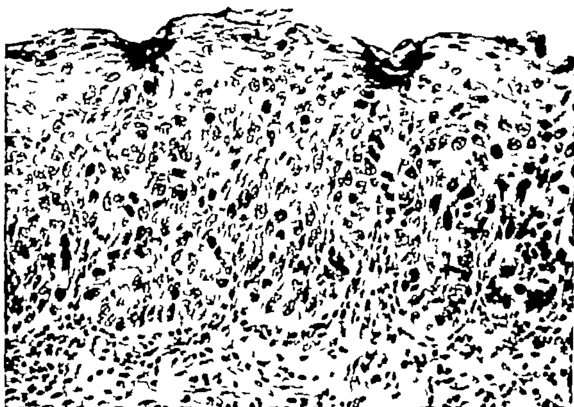


Fig. 139.—Epidermoid carcinoma in situ of the floor of the mouth. Note intact basement membrane, complete disorganization of the epithelium throughout all layers, and many mitotic figures. (×270.) (W.U. neg. 51-4661.)

Verrucous Carcinoma

Verrucous carcinoma is a form of epidermoid carcinoma with a distinctive morphologic pattern and clinical evolution. The intraoral distribution of this lesion and the usual squamous carcinoma seen at the Ellis Fischel State Cancer Hospital is shown in Table 4 (Ackerman).

Verrucous carcinoma occurs most frequently on the buccal mucosa and lower gingiva and is almost invariably associated with leukoplakia. It occurs predominantly in men who chew tobacco. This lesion may in time produce a large, fungating, soft, papillary growth (Fig. 140). It tends to become infected and to slowly invade contiguous structures. We have seen it destroy the mandible, grow through the soft tissues of the cheek, and invade the maxilla. Metastases

TABLE 4 DISTRIBUTION OF VERRUCOUS CARCINOMA BY SITE—ELLIS FISCHEL STATE CANCER HOSPITAL, COLUMBIA MO*

SITE	VERRUCOUS CARCINOMA	ALL CASES	RATIO
Bucca and lower gingiva	29	102	284
Upper gingiva and palate	7	31	226
Floor of mouth		25	
Tongue	1	45	
Total	37	203	182

*From Ackerman L. V and Johnson R Proc Second Nat Cancer Conf 1: 403 414 1952

from this tumor are exceedingly rare. The microscopic diagnosis may be difficult because of its well-differentiated character Sections of an adequate biopsy show swollen and voluminous rete pegs which extend into the deeper tissues, where their pattern becomes quite complex Once the pattern has been seen it can be recognized easily (Figs 141 and 142) Resection is the treatment of choice. If surgery or irradiation is inadequate the lesion will recur (Ackerman, 1948)

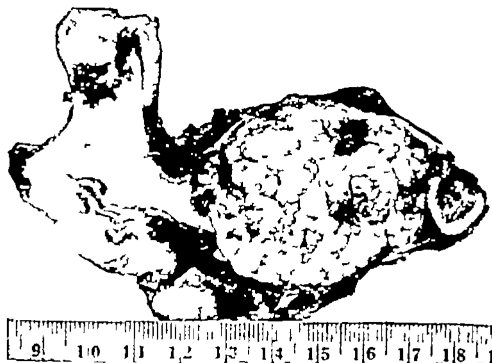


Fig 140—Gross photograph of extensive papillary verrucous carcinoma. (From Ackerman L. V and del Regato J A Cancer St. Louis 1947 The C. V Mosby Co)

Epidermoid Carcinoma

Ulcerating epidermoid carcinoma may begin in association with leukoplakia or as carcinoma in situ. It gradually forms an ulcer with firm, indurated borders Epidermoid carcinomas within the oral cavity are often only moderately well differentiated. In the base of the tongue or the nasopharynx they become quite undifferentiated (Fig 143) They quickly invade the lingual muscles and spread widely into surrounding structures Squamous carcinoma of the nasopharynx invades the base of the skull and often involves nerves. These undifferentiated squamous carcinomas metastasize mainly by lymphatics The distribution of lymph node involvement depends on the anatomy of lymphatic drainage for instance,

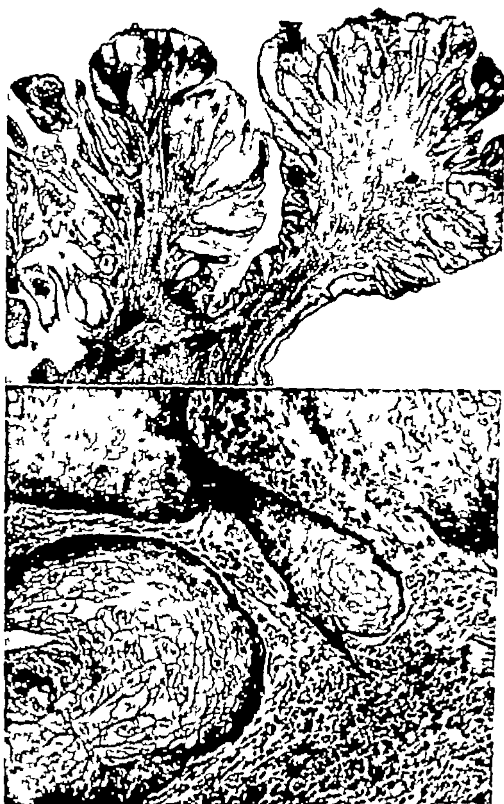


Fig 141 —Frondlike papillary verrucous carcinoma. (Low power)

Fig 142 —Detailed view of the swollen rete ridges of a deeply invasive verrucous carcinoma with intact basement membrane.



Fig 143.—Gross photograph of undifferentiated squamous carcinoma in the base of the tongue This patient presented with cervical metastases. The primary lesion shown was not discovered clinically because of the lack of proper palpation. This lesion was found after death (W U neg 50-371)



Fig 144.—Clinical photograph of a metastatic malignant tumor arising from the nasopharynx. (W U neg 48-4426)

the more anterior the lesion the lower down will be the lymph node metastases in the neck. Carcinoma of the tongue tends to give multiple small metastases which are not palpable. Carcinomas of the base of the tongue and the nasopharynx metastasize to the deep retropharyngeal lymph nodes (Fig 144) Treatment of lesions in the anterior two thirds of the tongue usually combines irradiation and neck dissection. Interstitial radium is placed in the tongue and a radical neck dissection is done on the homolateral side. About 25 per cent of the tongue lesions are cured by this procedure. Most verrucous carcinomas are cured by resection because of the low incidence of distant metastases Practically none of the squamous carcinomas of the nasopharynx and the base of the tongue are cured, the reasons for failure being the inability to sterilize the primary lesion locally by irradiation and the frequency of widespread metastases.



Fig 145 —Clinical photograph of a lymphosarcoma arising from the upper alveolus.

Lymphosarcoma

Lymphosarcoma most commonly occurs in the tonsil and in Waldeyer's ring of lymphoid tissue within the pharynx. It forms bulky masses which are very soft and cellular We have seen lymphosarcoma arise in the base of the tongue and from the upper and lower gingiva (Fig 145) The lesion shows the microscopic variations that are seen in lymphosarcomas elsewhere. This tumor may be associated with voluminous bilateral cervical lymph node enlargement. Irradiation therapy is capable of sterilizing both the intraoral tumor and the involved cervical lymph nodes.

Lymphoepithelioma

Lymphoepithelioma arises from the base of the tongue or the nasopharynx. The pathologic nature of this entity is debated. Some believe that it is a transi

tional carcinoma. Classically it consists of large clear cells with prominent nuclei and nucleoli and separated by lymphocytes. This lesion responds dramatically to irradiation therapy which cures about 25 per cent of all cases.

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Chapter 4

MANDIBLE AND MAXILLA

INTRODUCTION

The mandible and maxilla are discussed here because of the specialized nature of the lesions which occur within them and the intimate relation of pathologic changes within the oral cavity to these bony structures Salivary gland tumor and squamous carcinoma within the oral cavity may secondarily involve the maxilla or mandible, producing destructive bone lesions.

TRAUMATIC CYST

Hemorrhagic traumatic cysts of the mandible occur usually in young patients. Olech has reported 28 cases of which 8 were his own Pommer believes that the steady expansion of the hematoma following trauma is related to restricted venous drainage. For instance we know of a girl 11 years of age who following a tooth extraction developed swelling of the mandible over a ten-day interval. Roentgenogram demonstrated a large area of radiolucent destruction of the mandible (Fig 146) Unfortunately hemiresection of the mandible was done for an erroneous clinical and radiographic diagnosis of adamantinoma. Grossly the cystic space was filled with brownish yellow material and brown fluid. Microscopic examination revealed a shell of the cortex of the mandible. The periosteum adjacent to the dead bone showed prominent intramembranous new bone formation (see Fig 804) Cure could have been effected by unroofing the lesion and evacuating the blood.

GIANT CELL TUMOR

Giant cell tumor of the mandible and maxilla is a relatively uncommon neoplasm and, from the standpoint of pathogenesis, makes up a heterogeneous group. In 28 lesions of the jawbone reviewed by Waldron, 9 were probably variants of fibrous dysplasia, 14 were nonneoplastic, and in 5 the microscopic pattern was



Fig 146.—Roentgenogram of a traumatic cyst of the mandible in a girl 11 years of age. Note thin shell of remaining mandible. (W U neg 52 3857.)



Fig 147.—Clinical photograph of a young girl with an extensive giant cell reparative granuloma, almost completely replacing the maxilla. (Courtesy Dr A. I Murphy, Pittsburgh, Pa.) (W U negs. 58-268 and 58-267.)

similar to that of the giant cell tumor of the long bones The prognosis for all these lesions appears to be excellent none become malignant. The lesions designated as nonneoplastic have been referred to as giant cell reparative granuloma of the jaw by Jaffe (Fig 147) This disease affects children mainly girls, and occurs usually in the maxilla. Fibrous tissue hemorrhage, osteoid trabeculae and scattered giant cells are present (Radcliffe) Giant cell tumor produces a cystic lesion of the bone and usually occurs in young persons. Microscopically it shows large numbers of giant cells rather cellular vascular stroma, and often new bone formation (Fig 148) Giant cell tumor associated with hyperparathyroidism cannot be distinguished from one which is not. In fact a diagnosis of giant cell tumor of this region requires that hyperparathyroidism be ruled out (Black)

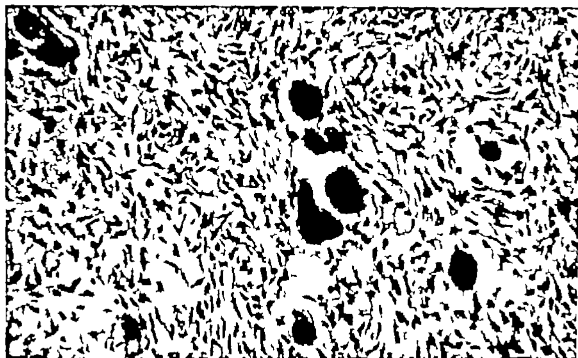


Fig. 148 —Photomicrograph of giant cell reparative granuloma with cellular fibrous tissue and collections of giant cells. (×400) (W U neg 58-4423)

FIBROUS DYSPLASIA (FIBROUS OSTEOMA)

Fibrous dysplasia of the mandible and maxilla occurs in young persons and causes diffuse enlargement of the mandible or maxilla. Radiographically there is an increased density if considerable bone formation is present. Decreased density results if the lesion is predominantly fibrous (Cahn) Disseminated fibrous dysplasia involving both jaws is a rare lesion which may be familial (McDonald) The microscopic picture varies from many spicules of new bone with a cellular vascular stroma to very dense bone (Billing) The more cellular types may be incorrectly diagnosed as osteosarcoma. In the past, Phemister recognized fibrous osteoma as benign and treated it conservatively Now it is considered to be a variant of fibrous dysplasia. This lesion has also been called osteofibroma or ossifying fibroma of the jaw Smith believes that osteoma and ossifying fibroma

(monostotic fibrous dysplasia) of cranial and facial bones are in the same clini and pathogenic group It does not become malignant and is not a true neoplas (See Bone, p 779) He demonstrated good correlation between the age of t patient and the maturation of the lesion We have seen a case with a long tir interval between surgical excisions, the first was highly cellular, very active, a could easily have been diagnosed as a malignant tumor, the second showed matu thick bone trabeculae in a relatively avascular stroma Sherman has shown t osteoma to be of cortical origin having distinct borders and an organized intern pattern (Figs 149 and 150)



Fig 119 —Ossifying fibroma in a Negro girl aged 17 years. Note sharp border of the lesic (Contributed by Dr C. A. Waldron, St. Louis Mo.)

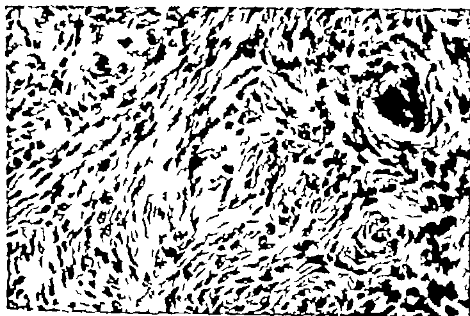


Fig 150—*Photomicrograph* of a cellular ossifying fibroma. Note well-differentiate character of individual cells with well-defined nuclei and small flecks of calcium. (×400 (W U neg 52-4084)

DEVELOPMENTAL CYSTS

Most cysts in the jaw are odontogenic. Robinson and Sonesson have clarific the classification of these cystic lesions. Their differentiation is of particular ir

terest to the oral pathologist. *Adamantinomas infrequently arise within them* Squamous carcinoma practically never occurs. The relative incidence of the different types of cystic lesions is illustrated in Table 5 Sonesson's data emphasizes the high proportion of radicular and primordial cysts.

TABLE 5 CLASSIFICATION*

I Epithelium-Lined Odontogenic Cysts	
A Nondentigerous	
Radicular cysts and primordial cysts	140
B Dentigerous cysts	
1 Pericoronal follicular cysts 2. Paradental follicular cysts	15
C. Cystic odontomas	3
II. Epithelial Odontogenic Tumours	
Adamantinomas	39
III Connective Tissue Tumours Odontogenic	
A. Central fibromyxomas	10
B Cementomas	1
Total number of odontogenic cysts and tumours	208

*From Sonesson A. Acta radiol. (supp. 81) pp. 1 159 1950

The inflammatory *radicular* cyst associated with infected tooth roots occurs either at the apex of the root or along its side if associated with an aberrant root canal. The residual type is seen in edentulous parts of the mandible or maxilla after extraction of a tooth. In Sonesson's series, over 50 per cent of the mandibular cysts and about 30 per cent of the maxillary cysts occurred in edentulous jaws. The *primordial* cyst (follicular cyst) occurs at an earlier stage in the development of the odontogenic epithelial formations than do dentigerous cysts. Radiologically it is often difficult to distinguish the radicular and primordial cysts microscopically it is impossible to differentiate them since they both are lined by stratified squamous epithelium.

Dentigerous cysts may be of the pericoronal type (originating from the dental follicle sac enclosing the entire crown and attached to the neck of the tooth) or the paradental type (with the cyst originating from the side of the crown perhaps near the cementoenamel junction, or from epithelial inclusions in or adjacent to the dental follicle sac) (Sonesson) Dentigerous cysts by definition contain a tooth or remnants of a tooth (Fig 151) They occur in young persons and are treated by excision. Microscopically they are lined by squamous epithelium and contain an imperfectly formed tooth (Fig 152) In most cases the tooth is fairly well formed enamel formation is almost invariably complete, and the roots are nearly so

Cystic odontomas originate from follicle sacs of malformed tooth germs. These cysts should be treated by enucleation. Vital teeth should be preserved. There is no reason to resect the mandible or maxilla. The complex composite odontoma contains calcified structures that bear little resemblance to the normal anatomic relation of the dental tissue. It contains variable amounts of enamel, dentine and cementum. This tumor is surrounded by a fibrous tissue capsule (Christensen) Pindborg reported a dentinoma, primarily an epithelial tumor usually located in the molar area of the mandible. This rare tumor often occurs

in connection with an impacted tooth It should be emphasized that other pathologic processes can mimic all the above cysts (adamantinomas giant-cell tumors salivary gland tumors or even metastatic carcinoma)

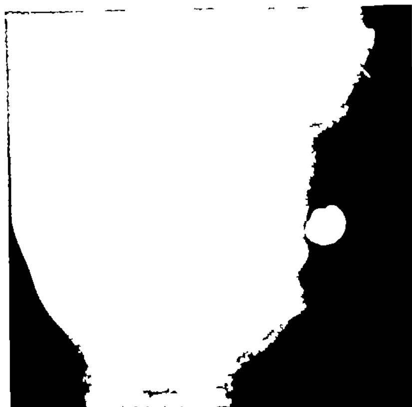


Fig 151 —Dentigerous cyst shown by roentgenogram. This large cyst occurred in a 15-year-old Negro girl. (EFSCH 13984)



Fig 152 —Gross photograph of a well-defined dentigerous cyst lined by stratified squamous epithelium and containing an imperfectly formed tooth. (W U neg 50-1915)

ADAMANTINOMA

Adamantinoma occurs mainly in the mandible. Occasionally it arises in the upper molar or premolar area where it may invade the antrum. It occurs in the mandible usually close to the angle (Sonesson) Forsberg believes that adaman

tinoma develops most frequently in the molar region because aberrant dental germs are most often found there. In 1036 cases reviewed by Small 52 per cent occurred in males 81 per cent of this group were located in the mandible. When first seen the tumor has often been present for several years (Fig 153) In Robinson's series the average age at onset was 38 years. It forms cystic areas of destruction which characteristically are lobulated (Sherman) (Figs 154 and 155) Other lesions may show multiloculations, such as giant cell tumor and metastatic carcinoma (Byars) Advanced adamantinomas may involve the entire mandible and extend across the symphysis They may arise within cysts (Cahn) (Fig 156)



153 —Clinical photograph of an adamantinoma which was allowed to reach this size over a period of twenty years. It involved the mandible on both sides and ulcerated through the surface

Microscopically adamantinoma mimics the enamel organ showing stellate reticulin which is continuous with tall columnar cells at the periphery Cystic change from degeneration of the stellate reticulin and focal areas of squamous metaplasia occur Large granular cells were present in two adamantinomas reported by Campbell. The treatment of choice is resection. All too often the lesion is enucleated rather than resected, and multiple recurrences follow We have seen recurrences extend over a twenty year period. A review of the sections from Schweitzer's case showed no differences between the usual adamantinoma and the one which metastasized (Fig 157) The metastases may have been a reflection of the long clinical course, inadequate treatment and ulceration. Implantation in Schweitzer's patient was a distinct possibility It probably is best to consider adamantinoma as only a locally invasive neoplasm. A high percentage of the



Figs. 154 and 155 —Roentgenogram and specimen of advanced adamantinoma Note xtensive involvement of the mandible with characteristic multiloculation. (Fig 154 W U neg 52-4760 Fig 155 W U neg 52-4635) (Specimen contributed by Dr L. T Byars St. Louis Mo)

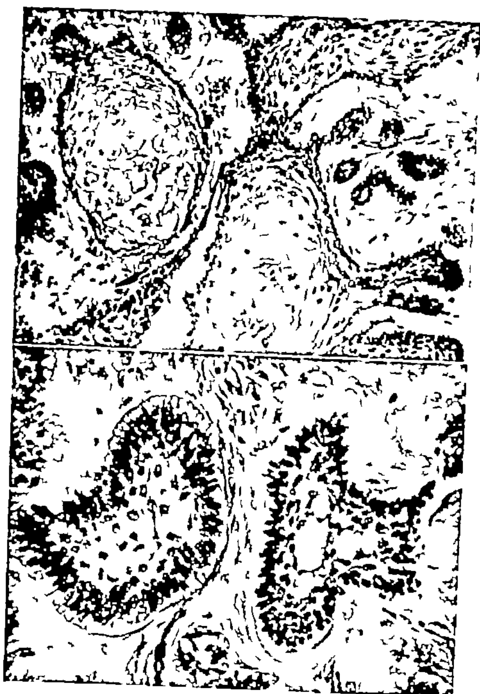


Fig 156.—Photomicrograph of an adamantinoma arising within a wall of a radicular cyst. It shows focal areas of squamous metaplasia. (×200) (W U neg 52 2576)

Fig 157—Photomicrograph of the metastasizing adamantinoma reported by Schweitzer This represents one of the surgical excisions. Microscopically it shows the distinctive pattern of the usual adamantinoma with the central areas suggesting stellate reticulum and the tall peripheral palisaded cells There is no microscopic evidence of malignancy (×360) (W U neg. 52-4086.)

cases reported in the literature as metastatic adamantinoma in reality are metastatic epidermoid carcinoma and metastatic malignant salivary gland tumors. Small emphasized that the soft odontoma or mixed odontogenic tumor should be separated from the adamantinoma because the soft odontoma is completely benign and does not recur

OTHER TUMORS OF THE MAXILLA

Papillary squamous metaplasia of the maxillary antrum is not neoplastic, but may entirely fill the antrum and be confused with a malignant tumor It is composed of well-differentiated squamous cells often intermingled with polymorphonuclear leukocytes. The basement membrane is intact (Eggston) (Fig 158) We have seen one instance of squamous carcinoma associated with this lesion



Fig 158.—Papillary squamous metaplasia of the lining of the antrum simulating squamous carcinoma. (Low power) (W U neg 52-5316.)

Carcinoma arising in the maxillary sinus has many patterns but usually it is undifferentiated squamous carcinoma (Ringertz) These carcinomas may arise in any part of the antrum and invade contiguous structures Frequently they cause loosening of the teeth and ulcerate into the oral cavity Adenocarcinoma of salivary gland origin also arises in the antrum. There are other types which defy classification, and the best description of these is that of Ringertz. Usually these cancers are advanced when first seen Their treatment by either well planned ir radiation or surgery often fails. Primary skin carcinoma both basal and epidermoid types may invade the maxilla.

METASTATIC CARCINOMA

Metastatic carcinoma may involve the mandible as a part of a disseminated process (Byars) We have seen it involved by tumors from the breast, thyroid

and prostate. Secondary involvement of the mandible by invasion is common from squamous carcinomas of the alveolar ridge the buccal mucosa and the floor of the mouth (Bairge) The tumor destroys the periosteum infiltrates beneath it, extends into the dental foramina and finally destroys the mandible. Squamous carcinoma metastatic to submaxillary lymph nodes can invade the mandible secondarily We have seen similar encroachment by primary malignant tumors of the submaxillary gland.

RARE LESIONS

Paget s disease of mandible and maxilla can occur as a dominant clinical ex pression of a generalized process (Ash) *Eosinophilic granuloma* causes a localized ragged zone of destruction more often in the mandible than maxilla *Mucoceles* of the maxilla may gradually expand and cause destruction of contiguous bones and thus be mistaken for a malignant neoplasm A melanotic benign pigmented tumor of the maxilla previously thought to be a variant of adamantinoma may in reality originate from *neuroectoderm* (Stowens) *Reticulum cell sarcoma* and *Ewing s sarcoma* may be primary in the mandible and in the cases we have seen they were incorrectly diagnosed radiographically as chronic osteomyelitis Every conceivable type of sarcoma can arise in either maxilla or mandible and we have observed *fibrosarcoma osteosarcoma* and *chondrosarcoma* In Kragh s 44 cases of osteogenic sarcoma of the jaws and facial bones the highest percentage was in the mandible. It was surprising that 11 of 35 patients were free from disease after a five year period No case arose in pre-existing Paget s disease, but several fol lowed previous irradiation.

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Chapter 5

RESPIRATORY TRACT

NOSE

Nasal polyps are not true neoplasms Their formation is associated with either infection or allergy These soft polypoid lesions tend to be bilateral. Microscopically they are composed of a loose mucoid stroma, mucous glands, and covered by respiratory epithelium They are infiltrated by lymphocytes, plasma cells and eosinophils. The presumably allergic polyps have, at times a marked eosinophilic leukocytic infiltrate With removal they tend to recur Rarely rather extensive squamous metaplasia of polyps is seen not only within the nasal cavity but also within the maxilla This papillary squamous metaplasia may be so abundant as to block the nares Microscopically the epithelium is well differentiated may show occasional mitotic figures and is invariably infiltrated with polymorphonuclear leukocytes. It is often incorrectly diagnosed as malignant. (See Fig 158) We have seen one polyp of the nasal mucosa, and one polyp of the maxilla eventually become epidermoid carcinoma.



Fig 159 —Adenocarcinoma of the nares in a 70-year-old man. This well-differentiated carcinoma was first incorrectly diagnosed as a benign polyp, but since then has stubbornly recurred over a four year period. (×210) (W U neg 52 595)

Rare truly malignant polyps assume the form of adenocarcinoma (Fig 159) They tend to recur after excision. These neoplastic polyps may grow slowly but they finally invade contiguous structures (Kramer)

The *nasopharyngeal fibroma* occurs invariably in young boys and can grow sufficiently to occlude completely the involved nares. It arises from the wall of the nasopharyngeal cavity or posterior nasal space (Fig 160) It may protrude below the free edge of the soft palate extend into the antrum (Martin) grow to the external orifice of the nares or posteriorly into the nasopharynx. These lesions tend to bleed severely on manipulation Microscopically they are made up of star shaped cells growing in a vascular stroma (Fig 161) These tumors infrequently

undergo spontaneous regression when the patient reaches maturity As these tumors occur primarily in males and are also age linked, they are undoubtedly influenced by some unknown endocrine factor (Sternberg)

Plasma cell tumors arising in the nasopharynx may present primarily in the nose as a soft bleeding mass Microscopic examination shows a typical plasma cell tumor These tumors invariably become disseminated plasma cell myeloma.

Basal cell carcinomas and epidermoid carcinomas of the skin may secondarily invade the nose and destroy the cartilage. *Carcinoma of the antrum* can also invade the nares. Rarely a *primary epidermoid carcinoma* of the nasal septum occurs.

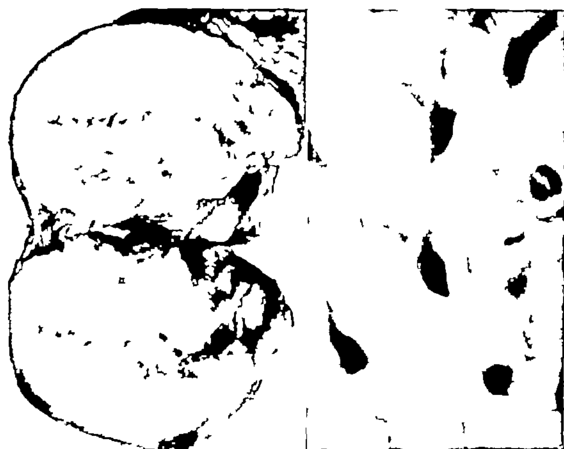


Fig 160 —Gross photograph of a large nasopharyngeal fibroma in a young man. (W U neg 48-4361)

Fig. 161 —Typical star-shaped cells of a nasopharyngeal fibroma growing in a vascular stroma. (High power) (W U neg 48-3889)

LARYNX

Infection

The commonest infection which involves the larynx is *tuberculosis* This process begins with interarytenoid edema followed by involvement of the true cord which may spread to involve a wide area of the larynx. Roentgenographic examination of the chest invariably shows active advanced tuberculosis. Laryngeal biopsy shows typical tuberculosis Chronic nonspecific *laryngitis* occurs, the changes

on biopsy are nonspecific. Other specific laryngitides are syphilitic, lepromatous, and fungal. We have diagnosed several cases of histoplasmosis and one of blastomycosis. Laryngeal granulomas due to endotracheal trauma caused by intubation can occur and be mistaken for a neoplasm (Barton).

Laryngeal Nodule

In people who misuse their voices, laryngeal nodules (a peculiar noninflammatory reaction to injury) causing hoarseness may appear. These nodules occur chiefly on the anterior third of the vocal cords. They have been variously called singers nodes, amyloid tumor, polyps, and varices. Microscopically they present varying patterns, depending on their stage of involution (Ash). Early, they are



Fig. 162.—Photomicrograph of a laryngeal nodule of the larynx. Note amorphous poorly stained material beneath the intact epithelium. (Low power.) (W U neg. 50-479.)

fibrinous and fibrous, and progress through adenomatous, vascular, and hyaline phases. The hyaline stage is the one previously designated amyloid tumor. This is a misnomer. True amyloid deposits do occur in the larynx in the systemic malady (Fig. 162).

Tumors

Papillomatosis.—Papillomatosis of the larynx is a disease (perhaps viral in origin) usually of childhood and adolescence in which multiple papillary tumors occur on the true cord and may involve the entire cord, false cord, and subglottic area (Ferguson). Because of its extent, it may cause extreme respiratory embarrassment and even death (Björk). Microscopic examination shows a papil

lary pattern with well-differentiated orderly cells (Fig 163) These tumors tend to recur over a long period of time but invariably maintain their orderly character Rarely, invasive squamous carcinoma develops in association with laryngeal papillomatosis (Walsh) We have seen two cases in which squamous carcinoma followed the presence of laryngeal papillomas of many years duration.



Fig 163 —Photomicrograph of papillomatosis of the larynx in a child. Note papillary character and excellent differentiation of the epithelium. (×120) (W U neg 58-235)

Keratosis.—Keratosis of the larynx involves the true cord. This lesion often occurs in smokers in singers and in those who use their voices excessively Examination shows a thickening of the vocal cord. Biopsy reveals hyperkeratotic epithelium with downgrowth of the underlying squamous cells (Fig 164) Foci of cellular atypia may be present. This lesion tends to persist and in time may progress to or be associated with cancer (Gordon) If there is any question about the diagnosis further biopsies should be taken (Clerf) We have seen a patient in whom 46 biopsies of the cord, taken over a ten year period, have shown hyper keratosis and epithelial hyperplasia without evidence of cancer

Carcinoma in Situ.—During the last few years epidermoid carcinoma in situ has been recognized as a definite entity This lesion in the larynx has the same

implication as it has in other organs It may occur at the peripheral margin of an invasive cancer or be present without invasion Patients with this entity have hoarseness and perhaps slight reddening of the true cord Biopsy shows epidermoid carcinoma in situ (Fig 165) Such a lesion may be cured by biopsy, local excision laryngeal fissure stripping or irradiation therapy In certain instances it may appear later on the opposite cord We also know that a significant proportion (perhaps 30 per cent) of invasive carcinomas *are associated with* in situ

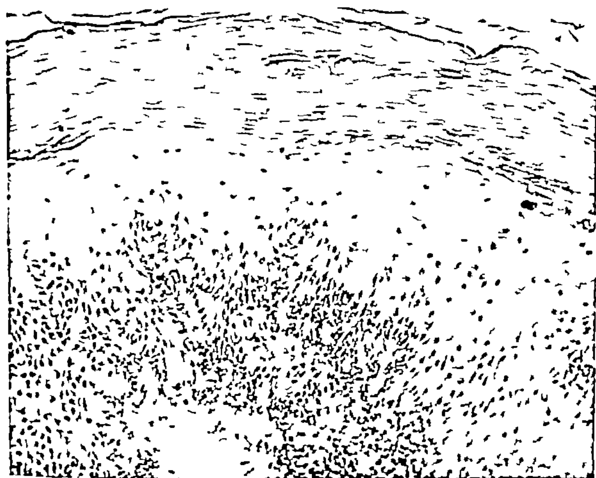


Fig 164—Photomicrograph of keratosis of the larynx with hyperkeratotic epithelium and acanthosis. The basal membrane is intact (×115) (W U neg 51 1320)

cancer We suspect that if this lesion is not treated, it will progress in time to invasive carcinoma, but the length of this time interval is unknown (Altmann) We know of several patients who have had carcinoma in situ for five to eight years without developing invasive cancer Careful evaluation of these cases (critical histologic appraisal, judicious therapy and adequate follow up) should clarify the status of this entity

Invasive Epidermoid Carcinoma.—Invasive epidermoid carcinoma occurs most commonly in men of the older age group It is the most common tumor of the larynx. It occurs in order of frequency on the anterior portion of the vocal cords the subglottic area, the base of the epiglottis the pyriform sinuses and in the aryepiglottic folds. Squamous carcinoma of the true cord is usually quite well

differentiated and tends to remain fairly well localized because of the surrounding cartilaginous wall and the paucity of lymphatics (Figs. 166, 167 and 168) Carcinoma in the subglottic area often spreads much more quickly to other areas and is advanced when first seen (Fig 169) Carcinoma of the larynx extends locally to involve surrounding soft tissues, muscle, and thyroid Contrary to former opinion cervical lymph node metastases occur in a significant number of these cases no matter what the location of the primary carcinoma.



Fig 165 —Photomicrograph of epidermoid carcinoma in situ of the larynx. Note *thickening of the epithelium with intact basement membrane and complete disorganization of* all layers (×?00) (W U neg 50 960)

The treatment of carcinoma of the larynx is by irradiation surgery, or some combination of these two Excellent results can be obtained by irradiation alone *in early carcinoma of the true cord (Lenz Harris) If irradiation fails surgery* can be performed later It must be emphasized that any irradiation must be done by a skilled radiotherapist The more advanced lesions of the larynx and the subglottic area are best treated by resection which may be combined with neck dissection if cervical node metastases are suspected.

Rare Tumors.—*Adenocarcinomas* of the salivary gland type (so-called cylindromatous) can arise from the mucous glands of the larynx. We have seen one in which the original biopsy was extremely well differentiated (Fig 170) yet metastases *to the regional nodes* and both lungs were present. We have also seen *lymphosarcoma* primarily involving the larynx, a single instance of a *carcinosarcoma bronchial adenoma* (carcinoid type) *benign chondroma* of the cricoid cartilage a *plasma-cell myeloma* with initial clinical manifestations in the larynx that later became disseminated (Costen) and an instance of *metastatic carcinoma* from the



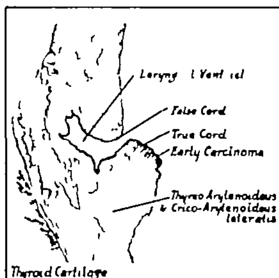


Fig 166—Sagittal section of a gross specim n of a larynx showing a small area of involvement of the true cord at the point marked by the arrow (W U neg 49-6450)

Fig 167—Schematic representation and anatomy of the lesion demonstrated in Fig 168. (W U neg 5? 4745)

Fig 168—Photomicrograph of the lesion illustrated in Fig 166 showing topography of the larynx and the superficial character of the carcinoma. This lesion could have been cured as well by good irradiation therapy as by laryngectomy (Low power) (W U neg 51 147)



Fig 169 —Advanced carcinoma involving both cords and the subglottic area. Note extensive involvement. Such involvement cannot always be appreciated on laryngoscopic examination. (Courtesy Dr Franz Leidler Veterans Hospital, Jefferson Barracks, Mo.)



Fig 170 —Photomicrograph of extremely well-differentiated adenocarcinoma arising from mucous glands of the larynx. Extensive pulmonary metastases were present at the time of this biopsy (×500) (W U neg 5? 4079)

kidney first causing laryngeal symptoms We have seen two instances of *granular cell myoblastoma* involving the true cord of the larynx Both of these were mistaken microscopically for epidermoid carcinoma because of the secondary pseudoepitheliomatous hyperplasia present in conjunction with the lesion

TRACHEA

Papilloma and *papillomatosis* of the trachea similar to the lesion seen in the larynx, can occur (Buffmire) (Fig 171) Small *adenocarcinoma* may arise from tracheal mucous glands and form a local mass which may be resectable (Vieta) Epidermoid carcinoma of the trachea is often secondary to direct extension of primary carcinoma of the bronchus or esophagus Rarely, however, primary epidermoid carcinoma can occur Cure by surgical resection has not been reported

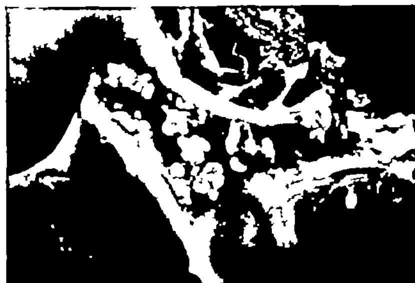


Fig 171 —Gross photograph of extensive papillomatosis of the trachea and bronchi. (AFIP 789980)

LUNG

Introduction

Since 1933 when the first lung was successfully resected for bronchogenic carcinoma, advances in thoracic surgery have been extremely rapid. As a result exploratory thoracotomy has become so safe that debatable lesions of the lung or bronchus are explored without hesitation. This chapter describes only those lesions pertaining particularly to surgical pathology and indicates the wide scope of this specialty

In an active thoracic surgery service the most common specimens result from segmental resections, lobectomy and pneumonectomy Unfortunately, some pathologists are content to make a simple diagnosis of tuberculosis, bronchiectasis, or cancer To extend the knowledge of pulmonary pathology and to give the surgeon more than a mere diagnosis it is necessary to have a well-organized method for fixing and studying the specimens In some instances it is necessary to obtain material for bacteriologic study before fixing the specimen. It is our custom to inject the specimen with formalin and, after it is fixed to dissect it with careful

regard to its anatomy. Using Jackson Huber's nomenclature we have devised stamps in order to identify the site of pathologic change (Fig 172). In this fashion the pathologist quickly gains a concept of the areas in the various lobes which are most commonly involved in different pathologic processes. If the lesion is carcinoma, sections must be taken at the limits of the dissection and all lymph nodes must be studied. Lymph nodes and special sections should be placed in separate bottles so that proper identification may be made on microscopic study.

It is imperative to have thorough bacteriologic study for the identification of various inflammatory and granulomatous processes. Fixed sections often hinder the identification of the tubercle bacillus, *Histoplasma capsulatum*, Brucella, and

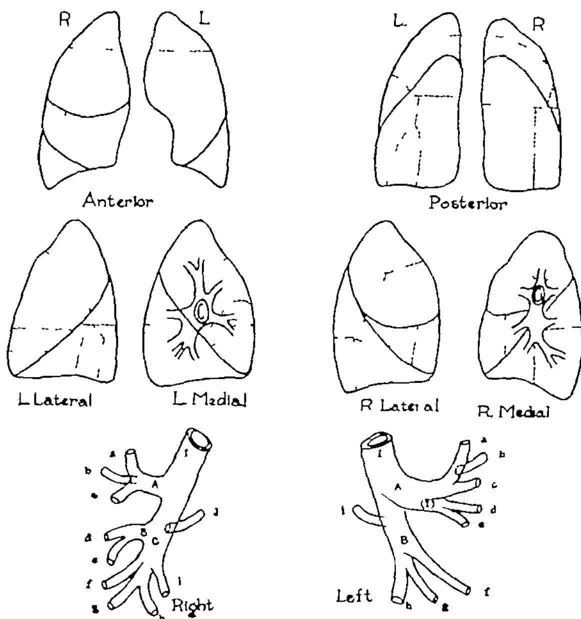


Fig. 172.—Diagrammatic sketch of the main branches of the bronchi of the lungs using the nomenclature of Brock and Jackson-Huber

(Legend continued on opposite page.)

other organisms. Weed has stressed that many granulomatous lesions which have similar microscopic patterns may be caused by a variety of agents. It has been our experience that tuberculosis occasionally has an unusual pattern which makes its true nature unsuspected. Therefore, material from any specimen containing pathology not yet diagnosed should be cultured.

Pleura

Obliterative Pleuritis and Decortication.—Inflammatory disease of the lung may involve the pleura. The pulmonary lesion may completely clear, but pleural symphysis may take place with prominent fibrous thickening (up to several centimeters) of the pleura. These changes were seen frequently during World War II following penetrating injury to the chest. The underlying lung parenchyma may be perfectly normal. Its expansion is prevented by the surrounding rigid and contracted "thickened pleura." This "thickened pleura" can be peeled away in many instances with marked improvement of the underlying pulmonary function.

During World War II an organizing hematoma often formed following a penetrating wound of the thorax. If this hematoma were allowed to remain for a long time decortication would be extremely difficult. If the chest were entered too early before cleavage planes could be established decortication was impossible. The three- to five-week interval was found to be ideal (Samson). It should be emphasized

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(Legend continued from opposite page.)

Brock's Nomenclature	Jackson Huber's Nomenclature
Right Bronchial Tree	*Right Bronchial Tree*
I. Main bronchus	
A. Upper lobe bronchus	
B. Middle lobe bronchus	
C. Lower lobe bronchus	
a. *Apical* bronchus, upper lobe	*Apical* bronchus, upper lobe
b. *Subapical* bronchus, upper lobe	*Anterior* bronchus, upper lobe
c. *Pectoral* bronchus, upper lobe	*Posterior* bronchus, upper lobe
d. *Medial* division, middle lobe	*Medial* division, middle lobe
e. *Lateral* division, middle lobe	*Lateral* division, middle lobe
f. *Anterior basal* bronchus, lower lobe	*Anterior basal* bronchus, lower lobe
g. *Middle basal* bronchus, lower lobe	*Lateral basal* bronchus, lower lobe
h. *Posterior basal* bronchus, lower lobe	*Posterior basal* bronchus, lower lobe
i. *Cardiac* bronchus, lower lobe	*Medial basal* bronchus, lower lobe
j. *Apical* bronchus, lower lobe	*Superior* bronchus, lower lobe
Left Bronchial Tree	*Left Bronchial Tree*
I. Main bronchus	
A. Upper lobe bronchus	
B. Lower lobe bronchus	
(1) Lingular bronchus	
a. *Apical* bronchus, upper lobe	*Superior division*, upper lobe
b. *Subapical* bronchus, upper lobe	*Apical posterior*, upper lobe
c. *Pectoral* bronchus, upper lobe	*Anterior* bronchus, upper lobe
d. *Upper division, lingular*, upper lobe	*Superior lingular, inferior division*, upper lobe
e. *Lower division, lingular*, upper lobe	*Inferior lingular, inferior division*, upper lobe
f. *Anterior basal* bronchus, lower lobe	*Anterior medial basal*, lower lobe
g. *Middle basal* bronchus, lower lobe	*Lateral basal*, lower lobe
h. *Posterior basal* bronchus, lower lobe	*Posterior basal*, lower lobe
i. *Apical* bronchus, lower lobe	*Superior* bronchus, lower lobe



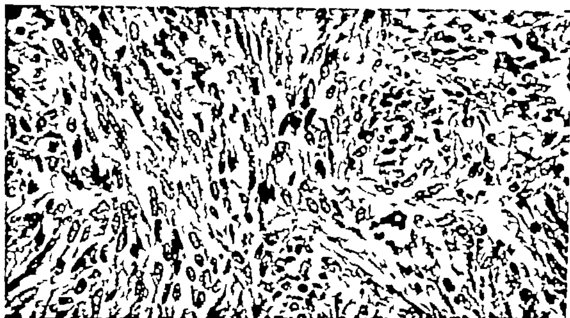


Fig 173.—Gross photograph of a large asymptomatic, benign fibrous mesothelioma of the pleura. (W U neg. 50-6554.)

Fig. 174.—Photomicrograph of a highly cellular fibrous type mesothelioma. These changes may be incorrectly diagnosed as sarcoma. (×460.) (W U neg 52 3455.)

that this material obtained by decortication represents an organized hematoma made up of fibrous tissue *without elastic tissue* which in itself is proof that the underlying pleura is not involved. Infection may cause hemo-organization to occur more rapidly. In patients with long standing pleural effusion bloody fluid used to be considered diagnostic of cancer and serous effusion as suggestive of tuberculosis.

The indication for resection in tuberculous bronchiectasis may be the bronchiectasis rather than the tuberculosis per se. With large thick walled persistent cavities in lung parenchyma with little active disease, resection is the treatment of choice (Fig 180) Because the wall of these cavities is often continuous with both layers of pleura and chest wall it is possible to effect only partial closure by conventional collapse procedures. Lower lobe cavities also often require resection. Frequently in patients who have had thoracoplasty for upper lobe cavities, these cavities persist in association with bronchiectasis The sputum remains abundant and positive for tubercle bacilli. Resection in such cases is well indicated. Thoracoplasty is rarely performed today Generally speaking resection should be done for any chronic stabilized process with some structural defect such as cavitation with positive sputum If the process is pathologically extremely active with little tendency toward fibrous encapsulation surgical interference will not halt the progress of the disease.



Fig 175 —Photomicrograph of tuberculosis involving a small bronchus with narrowing of the lumen ulceration and peribronchial involvement (Low power) (W U neg 49-5636)

Sweany reported his observations on 34 specimens in patients who had received rest and prolonged antimicrobial therapy He demonstrated that about 25 per cent of the advanced lesions showed healing by approximation of the walls of the cavities with granulation tissue followed by fibrosis and stellate scars. There was also a group of cases with advanced disease which became stabilized and left chronic open cavities It is potentially dangerous in a high percentage of cases when a cavity heals by inspissation of caseous material and there is a communicating bronchus (Auerbach) With the newer drugs cavities can completely or almost completely heal leaving a thin fibrous wall with a smooth surface. The inner lining of the cavity has no epithelium except at the point where the bronchus

enters the cavity In this zone it is squamous in nature. This method of healing is relatively rare (Thompson Auerbach) (Figs. 176 and 177)

Tuberculomas are relatively infrequent lesions. In 18 patients with such lesions seen at Barnes Hospital 11 were over the age of 40 (Black) These lesions



Fig 176—Gross photograph showing two apparently healed cavities of the right middle lobe (From Auerbach O and Small M J Am. Rev Tuberc. 75: 242, 1957)



Fig 177—Photomicrograph of lining of healed cavity shown in Fig 176. There is no epithelium and no evidence of activity of the process (Slide contributed by Dr O Auerbach, East Orange N J) (×260) (W U neg 58-128A.)

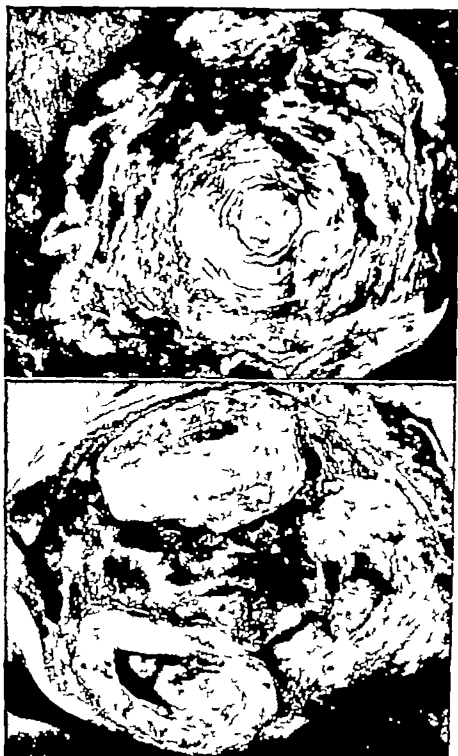


Fig 178 —Gross photograph of a large tuberculoma which elevated the pleural surface and presented a laminated appearance (W U neg 48-5597)

Fig 179 —Tuberculoma with central cavitation. These lesions may cause widespread pulmonary dissemination. (W U neg 48-5009)

are located immediately beneath the pleura and form discrete firm round masses The pleura overlying the *tuberculoma is white or slightly yellow in color* There are usually no pleural adhesions On section they may show concentric laminations of calcification (Fig 178) Infrequently they show areas of central cavitation (Fig 179) Evidence suggests that the tuberculoma is a reinfection process rather than a primary Ghon focus The large size subpleural location thick capsule presence of separate satellite nodules absence of bone and evidence in some cases of separate Ranke's complexes support this viewpoint Microscopically we have invariably found areas of *persistent caseation* Elastic and connective tissue stains outline the shadows of persistent alveoli demonstrating that this process is the end stage of a caseous lobular tuberculous pneumonia There is also prominent subpleural fibrous thickening In a few instances we have demonstrated communication of the process with a bronchus Small active tubercles may be present in

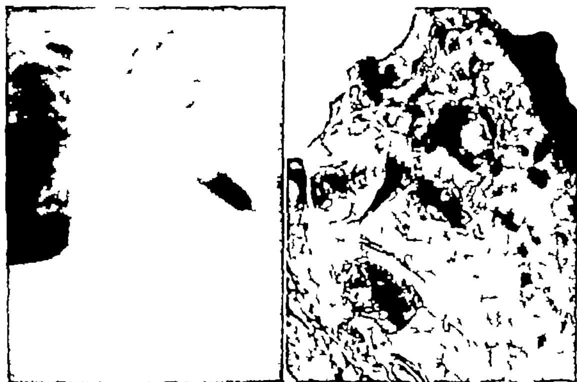


Fig 180—Extensive tuberculosis involving the entire left lung with prominent bronchiectasis, cavitation and thickened pleura It is obvious that compression therapy cannot cure such lesions. (W U neg 50-5757)

the immediate vicinity of the main lesion Lesions of an identical gross pattern may be caused by other organisms than the tubercle bacilli particularly by histoplasmosis and fungus diseases. In 35 surgically resected discrete pulmonary granulomas Zimmerman identified tubercle bacilli in 6 lesions coccidioides in 3 and histoplasma in 19 No organisms were found in the remaining 7

Radiologically it is impossible to differentiate tuberculomas from primary or secondary neoplasms The presence of concentric or focal areas of calcification strongly supports a diagnosis of tuberculoma. We have seen 2 carcinomas of the lung with focal calcification both incorrectly diagnosed radiographically as tuberculomas. Because these lesions contain persistent areas of caseation and cannot be differentiated from a neoplasm they must be resected Gross examination at operation is almost always diagnostic, but frozen section should be used to confirm it.

Lung Abscess.—Lung abscesses are most commonly located in the right lower lobe, right upper lobe, and left lower lobe according to a series reported from Barnes Hospital. The right side and the lower lobes were more frequently involved than the upper lobes (Bosher). However in Brock's series of 50 cases, the right upper lobe was involved in 20 the right lower lobe in 12, the left upper lobe in 7 and the left lower lobe in 8 Brock emphasized that the apical segments of the upper lobes are only rarely the site of an abscess. The subapical segment is the most common localization in the right upper lobe, and the axillary branch of the pectoral segment is the most common in the left upper lobe (Figs 181 and 182)



Figs 181 and 182.—Roentgenogram and gross specimen of a chronic multilocular abscess of the left upper lobe with surrounding organizing pneumonia. (Fig. 181 W U neg 50-419 Fig 182 W U neg 49-6443)

The anterior position of the middle lobe bronchus makes abscess in this lobe infrequent. The apical segment of the lower lobes is particularly vulnerable in the supine position The basal bronchi of the lower lobes are about equally susceptible. Brock points out that basal segment involvement by atelectasis and infection is frequent because of their dependency limited movement of the diaphragm and abdominal muscles, tight bandaging and excessive sedation and dehydration following abdominal operations.

The etiology and treatment of lung abscess have changed considerably with the advent of antibiotics. In the past, lung abscesses often followed tonsillectomies and operations in the throat but today this complication is relatively infrequent Lung abscess most frequently follows the aspiration of infected or foreign material. Embolism from a distant source does not cause unilocular abscess If emboli of infected material reach the lung there is usually bilateral sepsis. It must be

remembered that lung abscess may be secondary to a carcinoma. Brock reported 56 patients with abscesses secondary to carcinoma 53 were over the age of 45 years Thirty per cent of his patients over 45 had abscesses secondary to cancer In about one half of the cases the cause is unknown Frequently patients are seen first and treated by an internist Often the abscess clears particularly when it is small. Chronic abscesses are best treated surgically Today drainage by re section of a rib is seldom done. In small unilocular abscesses partial resection of the lobe may be curative (Myers) However Burford believes that lobectomy is preferable because complications such as bronchopleural fistula and empyema are much less frequent. The larger more complicated abscess is invariably associated with fibrosis and bronchiectasis of the lung In these cases lobectomy and occa sionally pneumonectomy are necessary

Grossly and microscopically chronic abscesses have thick fibrotic walls and are surrounded by areas of organizing pneumonia The bronchi communicating with them show prominent bronchiectasis. The clinical result of abscess resection is excellent. The mortality rate in the cases treated by Harter was under 5 per cent.

Complications of untreated lung abscesses include brain abscesses empyema exsanguinating hemorrhage, overwhelming toxicity and spread of the process The newer methods of treatment have greatly reduced the frequency of these complications

Miscellaneous Infections.—There are many granulomatous processes which become focal and chronic within the lung and which are usually resected because of the difficulty in differentiating them from neoplasms Frequently all one can say after studying these lesions is that the process is a chronic granulomatous one. We have come to realize that various bacteria and fungi can give similar microscopic patterns and have made it our custom in all debatable lesions of the lung to put small pieces of tissue into the refrigerator so that if the permanent sections are not diagnostic, this material may be thoroughly studied bacteriologically By this procedure we have found unexpected tuberculosis, histoplasmosis blastomycosis and other diseases The recognition particularly of fungi is aided by the use of the Schiff stain it selectively stains the capsule of the organism

Broncholiths.—Broncholiths occur rather infrequently They are usually produced by erosion of partially calcified tuberculous lymph nodes into the bron chial lumen. In bronchiectasis bronchial cartilage may undergo ossification and ulcerate into the lumen (Schmidt) (Fig 183)

Lipoid Pneumonia.—Lipoid pneumonia is often a complication of debilitating disease or an incidental postmortem finding However, the local expressions of this process are often confused particularly with malignant neoplasms and con sequently have become a surgical problem Lipoid pneumonia can be divided into two types the exogenous and the endogenous. In the exogenous type lipoid reaches the lungs in various ways (oily nasal sprays cod liver oil and mineral oil) We have seen one instance of partial esophageal obstruction which facilitated aspiration of oily medication. The patient's symptoms may warrant radiographic examination which may show either a well-defined or a diffuse pulmonary process

Examination of the sputum for the presence of fat particles is not diagnostic. Peculiar appearing macrophages may be seen in the sputum and be confused cytologically with carcinoma. At the time of exploration a localized lesion of lipoid pneumonia may be extremely firm. The lymphatics over the surface of the lung are often prominent suggesting lymphatic permeation by carcinoma (Fig 184) The surgeon may see fat droplets if he cuts across one of these lesions.

The microscopic pattern shows fibrous tissue and sudanophilic material filling large spaces (Fig 185) Frozen section may be difficult to interpret in the rare instance where there is proliferation of septate cells (Fig 186) These changes are similar to those described by Pinkerton in experimental animals. He has described methods of recognition of the various types of oils within the lung



Fig 183 Gross photograph of extensive broncholiths associated with advanced bronchiectasis. (W U neg 48-4214)

In endogenous lipoid pneumonia there are yellow areas which show by stain large amounts of lipid in the lung These changes we designate as endogenous because they are usually associated with some degree of bronchial block and represent merely the appearance of fat of endogenous origin The pathologist should be aware of this possibility for such localized areas of lipoid pneumonia may be present peripheral to a blocked bronchus due to a carcinoma. In one patient in whom there was bronchial block frozen section showed lipoid pneumonia which was locally excised. Later the patient returned with an obvious carcinoma of the bronchus The lipoid pneumonia had been secondary to this carcinoma.

Organizing Pneumonia.—Organizing pneumonia is not usually considered a surgical problem. However, if pneumonia instead of resolving organizes shadows occur in the lung which may be mistaken for tumor (Fig 187) We have seen 15 examples of persistent lesions in various areas of the lung (often in the upper lobe) in which patients had cough hemoptysis and weight loss justifying a clinical diagnosis of carcinoma (Ackerman) Radiographically the diagnosis is often carcinoma. Cytology studies in these cases were negative At the time of exploration the involved area was extremely firm and a diagnosis of organizing pneumonia was made only after frozen section Grossly the lobes contain yellow



Fig 184 —Gross photograph of exogenous lipoid pneumonia producing a firm indurated area which was grossly considered to be carcinoma. (W U neg 48-5291)

areas are very firm, and the pattern of the lung persists The process extends to the pleura which is invariably thickened Microscopically the exudate is organized, and the cellularity of the connective tissue depends on the duration of the process. Necrotizing lesions of small and moderate sized bronchi are present Bacteriologic study has not been rewarding

Bronchiectasis.—Bronchiectasis is a disease usually contracted in the first two decades of life (69 per cent of a large group studied by Perry) In a series of cases of bronchiectasis in children reported by Field there was a history of pneu

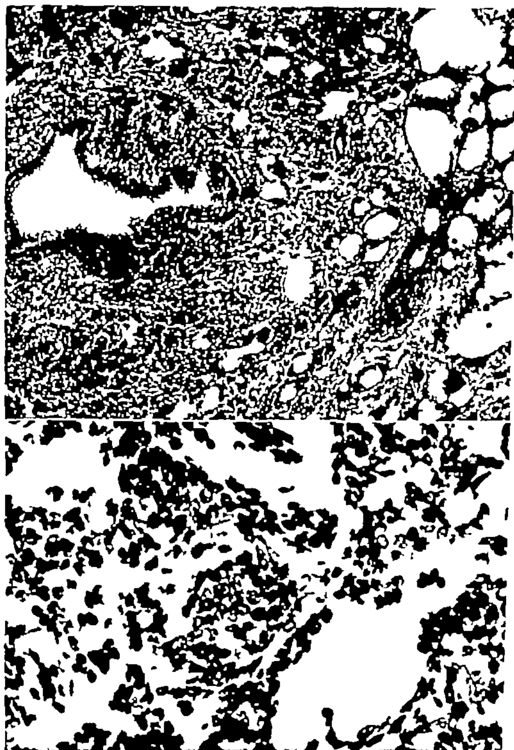


Fig. 185.—Photomicrograph of exogenous lipoid pneumonia demonstrating fibrosis and empty spaces representing sudanophilic material. (Low power.) (W U neg 48-3873.)

Fig 186.—Photomicrograph of proliferation of septate cells in lipoid pneumonia. The interpretation and potentiality of such areas is extremely difficult to evaluate. (W U neg 48-3774.)

monia in 35 per cent and pertussis in 30 per cent Bronchiectasis involves the left side more often than the right, possibly because the right side is better drained It is thought that the pulmonary artery constricts the left bronchus There is a syndrome of sinusitis, complete situs inversus, and bronchiectasis (Mallory) Sinusitis has often been incriminated as the cause of bronchiectasis but this concept lacks proof since sinusitis follows just as often as it precedes bronchiectasis.



Fig 187—Roentgenogram demonstrating hilar mass considered radiographically to be bronchogenic cancer but proved pathologically to be organizing pneumonia. (W U neg 52 7380)

The pathogenesis of bronchiectasis appears to be well established and probably represents more than one factor In the presence of pneumonitis there may be atelectasis but without infection bronchiectasis does not occur (Anspach) Probably the sequence of infection pneumonitis atelectasis and bronchiectasis is most common. Bronchiectasis is only rarely associated with amyloid disease With atelectasis intrapleural pressure rises. This negative pressure is transmitted through the solid nonexpanded pulmonary tissue to the elastic and expansible bronchial walls (Andrus) This sequence may be initiated by foreign bodies or by any process partially occluding the bronchial tree. With infection the regional

lymph nodes are often greatly enlarged (Ogilvie) Infection without atelectasis or pneumonitis is rarely a factor for the development of bronchiectasis (Mallory) The lower lobes are most commonly involved, and the lingular branch of the left upper lobe is usually involved with involvement of the left lower lobe. Lander points out that with collapse of the left lower lobe the lingular bronchus is displaced and with collapse of the right lower lobe drainage of the right middle lobe and pectoral branch of the right upper lobe is affected When bronchiectasis has been well established in an area of the lung it usually remains confined to that area. *Spread rarely takes place* unless there is additional pulmonary infection and atelectasis.

Grossly the pleura frequently is thickened and the lung is heavier than normal. Bronchiectasis is broadly classified into saccular or cystic type, and cylindrical type (Figs 188 and 189) The walls of the bronchi are thickened and dilated at times they widen to include abscesses, and infrequently there is pleural perforation and empyema. The intervening lung parenchyma shows variable degrees of damage. In minimal damage there may be no gross changes in prominent damage there is excessive fibrosis The involvement invariably is in the bronchi of the lower lobes In a high percentage of instances the process is bilateral. If the disease involves the left lower lobe, the lingular branch of the left upper lobe is almost always involved.

Microscopically bronchiectasis is usually well delimited the individual bronchi at times show ulceration of their surface epithelium. Metaplasia of the epithelium to a squamous type is infrequent, the epithelium usually remaining with persistent cilia. The submucosa demonstrates chronic granulation tissue. With advanced bronchiectasis the cartilage is fragmented or destroyed, and the muscularis mucosae is erased or associated with focal hyperplasia. Particularly in the younger patients there is an excess of lymphoid tissue around the bronchi which may contain germinal follicles (Fig 190) The mucous glands are not changed Communications are common between the bronchial and pulmonary arteries and the bronchial arteries are often greatly enlarged tortuous, and thick walled (Liebow) Anastomoses of the bronchial artery and pulmonary artery are found along the branches of the bronchi of the fourth order The changes in the lung parenchyma vary from none to advanced organizing pneumonia and fibrosis.

Clinicopathologic Correlation.—Patients with bronchiectasis have foul fetid abundant sputa. In the past, the only really effective treatment was surgical resection Before the use of antimicrobial drugs the majority of those patients who contracted the disease before the age of 10 and were not treated surgically died before the age of 40 The complications of bronchiectasis such as brain abscess and bronchopleural fistula with empyema are infrequent today Burford believes that surgical resection is indicated in patients with predominant unilateral disease and in those patients with hemorrhage and repeated pulmonary infections. In most instances, however conservative treatment with the newer drugs is sufficient to control the disease It is important to realize that the process is focal, and the local extent of the disease is entirely dependent upon the primary insult. For instance, in 114 patients reported by Perry only 6 developed a spread of disease all 6 had had intercurrent pneumonia.



Fig 188 —Gross photograph of extensive bronchiectasis involving the entire right lower lobe with diffuse parenchymal involvement (W U neg 49-5677)

Fig 189 —Gross photograph of saccular bronchiectasis of the subapical segment of the right upper lobe (W U neg 48-6736)

Cystic Disease.—Blebs are formed by rupture of an alveolus directly beneath the pleura with escape of air into the areolar layer of the pleura. This bleb may rupture into the free pleural space, causing pneumothorax. A bulla results from rupture of an alveolus into adjoining alveoli. A large air space may be formed from the continued accumulation of air and will be covered by a stretched thin pleura. The symptoms of such bullae depend upon compression of residual non diseased lung and may be complicated by hemorrhage and infection. Large cysts can be treated by simple excision of the walls with closure of bronchiolar fistulas and obliteration of the pleural space (Allbritten) Obstructive emphysema with



Fig 190—Photomicrograph of bronchiectasis. The epithelium is still present. There are diffuse chronic inflammation and absence of the muscularis mucosae and the bronchial cartilage is fragmented. (Low power) (W U neg 48-4907)

cyst formation can occur in young children on the basis of many causes. These causes include mucosal folds, plugs of mucus and deficiencies in the bronchial cartilages. Invariably the cysts occur only in the upper lobes and middle lobe. *Perhaps the abdominal muscles contract the lower lobes more forcibly than the* upper lobes (Jewsbury)

Congenital cystic disease is often incorrectly diagnosed. It certainly exists, for such lesions have been found at birth. The criteria for its recognition are poorly defined The absence of coal pigment in cystic areas is not absolutely diag nostic. The presence of other abnormalities of the bronchi are helpful but are not certain indications of the congenital nature of the lesion. It must be remem bered that a chronic lung abscess may completely heal, leaving a large unilocular

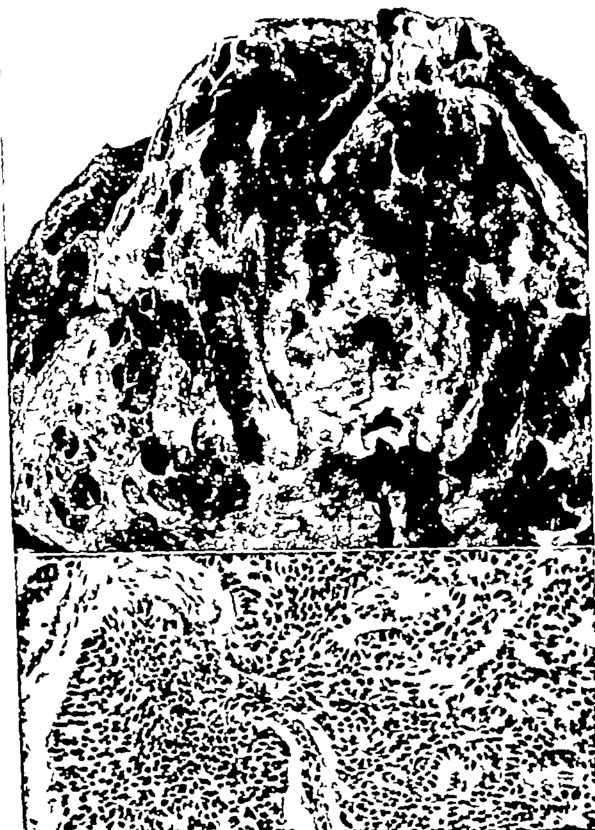


Fig 191.—Gross photograph of congenital cystic disease of the lung with numerous small honeycombed cavities involving the lung parenchyma. (W U neg 49-4531)

Fig 192.—Photomicrograph of a focal area of atypical epithelial proliferation occurring in congenital cystic disease (×240) (W U neg 50-3844)

cyst with smooth lining If there is no history suggesting lung abscess and if there are multiple lung cysts (Fig 191) a diagnosis of congenital cystic disease should be considered. In addition, in such lungs there may be focal areas of atypical epithelial proliferation supporting Womack's concept that congenital cystic disease is associated with an increased frequency of carcinoma (Fig 192) Korol reported 10 instances of cancer of the lung arising in zones of congenital cystic emphysema.

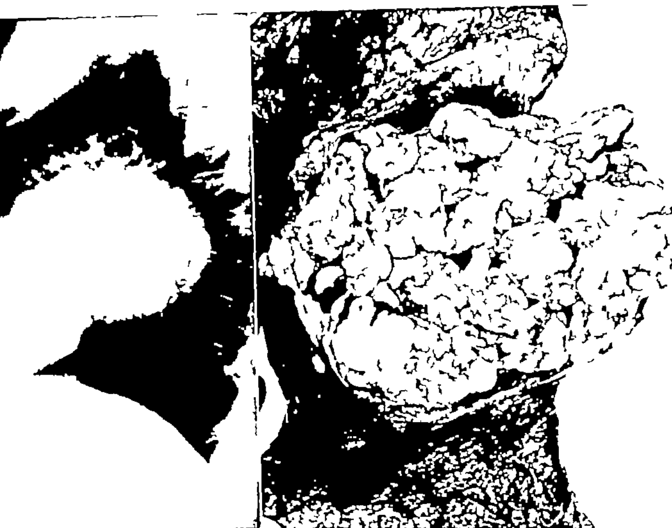
Intralobar Bronchopulmonary Sequestration.—Intralobar bronchopulmonary sequestration is a definite clinical and pathologic entity There is partial or complete developmental separation of a portion of a lobe of the lung without continuity with the bronchial tree. The posterior basal region of the lower lobe is the segment usually involved This segment is supplied by a large artery arising from the aorta just above or below the diaphragm Pryce believes that the persistence of the anomalous artery is the primary cause of this anomaly The area of sequestration often becomes cystic, and inflammation within it is common. Shunts between the anomalous arteries and intrapulmonary vessels have been demonstrated (Johnson) The failure to recognize the abnormal location of the vessel has resulted in deaths from hemorrhage This abnormality may be associated with other congenital alterations (Bruwer)

Benign Tumors of the Bronchi and Lung Parenchyma

Hamartoma (Chondroma)—The hamartoma (often called chondroma) is a relatively rare tumor which usually occurs in adults (McDonald) It is almost invariably located in the lung parenchyma just beneath the pleura. It varies in size from a small lesion to a mass occupying the entire lobe. It is sharply delineated and lobulated. On cross section the appearance is characterized by glistening nodules of cartilage (Figs. 193 and 194) We have seen one large hamartoma growing in the hilum fragments of this lesion were obtained through the bronchoscope. The patient finally died of infection secondary to the tumor This lesion is a frequent finding in the subpleural area at postmortem examination Microscopically it contains islands of cartilage with definite perichondria which often show calcification and rarely ossification. Anthracotic coal pigment is absent. This lesion has been designated as a hamartoma because it conforms to the definition of this term by Albrecht Hamartomata are tumor like malformations in which occur only abnormal mixing of the normal components of the organ The abnormalities may take the form of a change in quantity arrangement, or degree, or may comprise all three The hamartoma is made up of normal cartilage arranged in islands fat smooth muscle and islands of epithelium. At times this epithelium may be ciliated These elements are intermingled throughout the tumor This lesion is often discovered at x ray examination as a clear-cut shadow It is diagnosed easily by its gross appearance and should be treated by conservative resection.

Cavernous Vascular Lesions (Arteriovenous Fistula)—Cavernous vascular lesions (arteriovenous fistula) are fair sized and frequently multiple, occurring often in the right lower and middle lobes. These probable congenital lesions are

made up of huge vascular channels with arteriovenous communications (Lindskog) Microscopically the vessels are abnormal often showing deficiencies and excesses of muscle making it impossible to differentiate artery from vein (Liebow) Because of the shunt there is bruit cyanosis polycythemia, and low oxygen content of arterial blood Excision is curative.



Figs. 193 and 194—Roentgenogram of large well-delineated hamartoma of the lung Gross specimen demonstrates typical nodules of cartilage on cross section. (Fig 193 W U neg 49 2120 Fig 194 W U neg 49 1756)

Malignant Tumors of the Bronchi and Lung Parenchyma

Exfoliative Cytology—Exfoliative cytology has reached a high level of accuracy since Wandall's classical monograph. By examination of the sputum and/or bronchial secretions it is now possible to make a diagnosis in about 80 per cent of the patients with cancer while bronchoscopic biopsy in operable carcinoma of the lung is positive in only one third of the cases. Herbut has been successful with bronchial washings but we have found sputum to be more accurate and more easily obtained (Spjut) Tumors cells are at times easily recognized because they occur in clumps or there are numerous single bizarre cells (Figs. 195 197 and 198) Recognition becomes more difficult in the small-cell carci

noma in which individual cells may suggest lymphocytes rather than tumor It is imperative that fresh material be obtained from the lung, at least three specimens should be examined. In our experience the second specimen materially increases the percentage of positive diagnoses. The diagnosis of such exfoliative material should be on a conservative basis. Our reports are made as follows insufficient material, negative, suspicious but not diagnostic, or positive for cancer cells. In the suspicious but not diagnostic group we may see cells which are suggestive of cancer but this finding is to us an indication for repeat examination

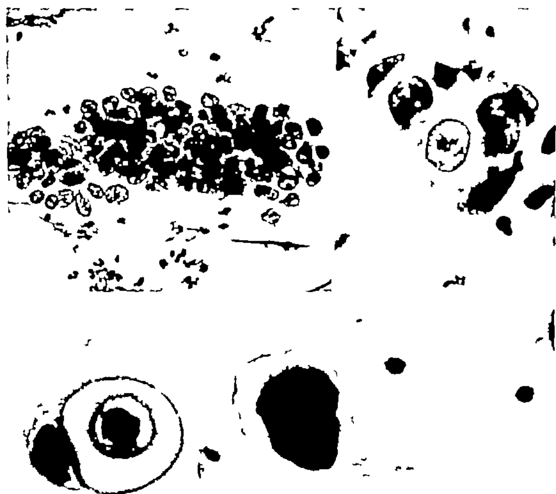


Fig 195 —A clump of malignant cells from the sputum in a patient with undifferentiated carcinoma. Note prominent nucleoli. (×320) (W U neg. 48-3883)

Fig 196 —Photomicrograph of a clump of macrophages mistaken for a malignant tumor Resection of the lobe demonstrated only lipoid pneumonia. (×1080) (W U neg 48-4588)

Fig 197 —Photomicrograph of a single cell showing cannibalism. This type of cell is invariably diagnostic of epidermoid carcinoma. (×1440) (W U neg 49-77)

Fig 198 —Photomicrograph of a single malignant tumor cell with giant deeply staining nucleus and "tadpole" pattern. This cell is only seen with epidermoid carcinoma. By cytology the pathologist can definitively diagnose the specific type of lung cancer in 80 to 90 per cent of the patients (1575) (W U neg 50-3181)

With these conservative diagnoses we have not made a false positive diagnosis in the past three years Earlier we had false positives in a case of lipoid pneumonia and in one of fungus disease (Fig 196) Macrophages are particularly confusing In patients who have either a negative or no bronchial biopsy, cytology is of great value in demonstrating cancer cells (Table 6) In 59 such cases, 13 frozen sections were requested and 11 demonstrated cancer Thus 48 patients having pulmonary resections had a positive cytology as the only positive preoperative tissue diagnosis Cancer was present in every instance (Spjut)

TABLE 6 CYTOLOGY AND BIOPSY IN OPERABLE CASES*

	POSITIVE CYTOLOGY	NEGATIVE OR SUSPICIOUS CYTOLOGY
Positive bronchial biopsy	35 (17 7%)†	25 (12 6%)
Negative bronchial biopsy	18 (9 1%)	20 (10·1%)
No bronchial biopsy	41 (20 5%)	59 (30 2%)

*From Spjut, H J., Fier D J., and Ackerman L. V J Thoracic Surg. 30: 99 107 1955

†Note The percentages are computed for the entire group The cytology is reported as a case.

Bronchoscopic Biopsy —Tissue obtained at the time of bronchoscopy may be insignificant in amount because of the timidity of the bronchoscopist or the inaccessibility of the lesion. *A biopsy should be fairly generous in spite of the* fact that we have a times seen pulmonary parenchyma and even mediastinal pleura in bronchoscopic biopsies no untoward effects have resulted from this *Only when small blood vessels are severed* is there any trouble. The fragments obtained should be quickly put in fixative The tissue should be sectioned at various levels for frequently tumor will be found at one level and not at another Still more rarely the biopsy may be taken from the edge of the tumor and epidermoid carcinoma in situ may be observed (Fig 199) If longitudinal furrows have be come obliterated or if there is *thickening granularity* or a nodular appearance of the mucosa, this may indicate carcinoma in situ (Wierman) On several occa sions we have also seen clumps of neoplastic cells apart from the bronchoscopic biopsy and on these we have been able to make a cytologic diagnosis of carci noma (Fig 200) The presence of squamous metaplasia in a biopsy specimen merely means that some form of inflammatory process is present which may or may not be combined with carcinoma (Fig 201)

Frozen Section Biopsy —Frozen section is an important procedure in debatable lesions of the lung and has its greatest value in peripheral lesions. If a patient has a resectable cancer of the lung the bronchoscopic biopsy will be positive in only 30 per cent of the instances. Cytologic examination will raise this percentage to 80 per cent only if an adequate number of specimens (3) are studied. This means that there will be a number of patients with or without cancer who have debatable lesions in the lung At the time of *exploratory thoracotomy* it is unwise to incise such a lesion, for if it proves to be cancer tumor cells may be implanted on the pleural surface. We have studied pleural washings under these circumstances and demonstrated *apparently* viable cancer cells (Spjut) It is our policy to excise debatable lesions with a margin of normal lung this excision may imply lobectomy

Frozen section is then done. Frequently the lesion proves to be a benign process such as tuberculoma hamartoma or organizing pneumonia. If it is cancer the thoracic surgeon decides the extent of resection.



Fig 199 —Photomicrograph demonstrating epidermoid carcinoma in situ of the bronchus. There is an intact basement membrane with disorganization of all layers. There was invasive carcinoma in another area. (×600) (W U neg 51 2748)

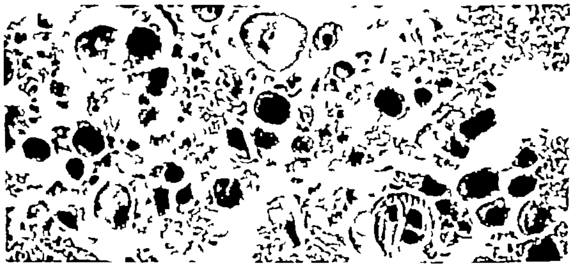


Fig 200 —Photomicrograph of a clump of malignant cells seen with a bronchoscopic biopsy Note variation in cell size and atypical nuclei (600) (W U neg 5? 3604)

It is much more important that the pathologist make a definitive diagnosis in lesions of the lung than in lesions of the breast for a second thoracotomy carries with it considerable morbidity and additional risk He must not be misled into making a diagnosis of carcinoma in highly cellular inflammatory lesions in organizing pneumonia or especially in lipoid pneumonia. Conversely some of the

poorly differentiated neoplasms of the lung may have a considerable inflammatory infiltrate and be incorrectly diagnosed as nonneoplastic.

Biopsy of Lymph Nodes and Lung Parenchyma.—Needle biopsy of the lung is used only for advanced inoperable lesions to confirm the diagnosis. We do not use it to diagnose disseminated bilateral diseases of the lung because it is inaccurate and may cause pulmonary complications. Implantations of cancer also occur in an operable lesion. There have been numerous procedures devised to diagnose bronchogenic cancer from lymph nodes outside the thoracic cage; if these nodes contain cancer or some other pathologic process, these findings negate thoracotomy. Daniels devised a procedure for exploration of the lymph nodes in



Fig 201.—Photomicrograph of prominent squamous metaplasia of the bronchus. (Low power.) (W.U. neg. 48-4908.)

the prescalene fat pad. Harken further extended this procedure to obtain nodes from the mediastinum. In 142 such explorations, a positive tissue diagnosis was obtained in 45 (32 per cent). These 45 patients were spared the risk and discomfort of a thoracotomy.

With bilateral disseminated diseases of the lung, biopsy of the scalene fat pad may be diagnostic. In some cases, however, direct biopsy of the lung under local anesthesia through an intercostal incision may be necessary when the scalene node biopsy is negative. A group of such cases has been reported by Klassen.

Carcinoma, Grade 1 (So-Called Bronchial Adenoma).—The so-called bronchial adenoma has been a much debated neoplasm. It is a relatively infrequent tumor, making up less than 5 per cent of all neoplasms of the bronchi. It is an

important neoplasm however for it is resectable and curable in a high percentage of instances. In Moersch's series, there were 45 males and 41 females the average age of the men being 42 years and of the women 38 years. These tumors commonly arise in the main stem bronchi but may be found in the smaller ramifications of the bronchopulmonary tree they are seldom entirely intrabronchial. In our group of 53 cases the most superficial tumor was firmly fixed below the level of the cartilaginous rings In a few instances about half the tumor was within the bronchus and the other half outside the bronchus. In most instances, however the bronchial component microscopically was only a small fraction of the entire





Fig. 202.—Gross photograph of a large so-called bronchial adenoma in which there is a large extrabronchial component. (W U neg 48-6250)

Fig. 203.—Gross photograph of a so-called bronchial adenoma with a prominent intra- and extrabronchial component. (W U neg 49-1827)

neoplasm (Fig 202) Usually the bronchial epithelium is not ulcerated (Fig 203) However with increased growth, with biopsy and with infection, superficial ulceration may occur The lack of ulceration is the reason tumor cells from bronchial adenomas are not recognized in the sputum or bronchial secretions. We have found such cells twice in cases with ulceration of the tumor Biopsy is usually positive in these cases (75 of 78 cases reported by Moersch) These tumors grow slowly but may become so large that they extend all the way to the pleura (Maier) Frequently they invade and destroy bronchial cartilage, and rarely they directly invade or metastasize to regional lymph nodes. Involvement of regional lymph

nodes occurred in 20 per cent of Meissner's cases. Local invasion of surrounding structures can occur and we have seen the myocardium invaded in one case (Black) On section the tumor is extremely vascular and often grayish yellow in color, at times with fibrous septa. This vascularity may lead to excessive hemorrhage on biopsy The histogenesis of this tumor has been in doubt, but majority opinion holds that it has origin from cells lining the mucous glands and ducts. Credit should be given Graham for insisting that this tumor has invasive characteristics and the capacity to metatasize locally and at times distantly

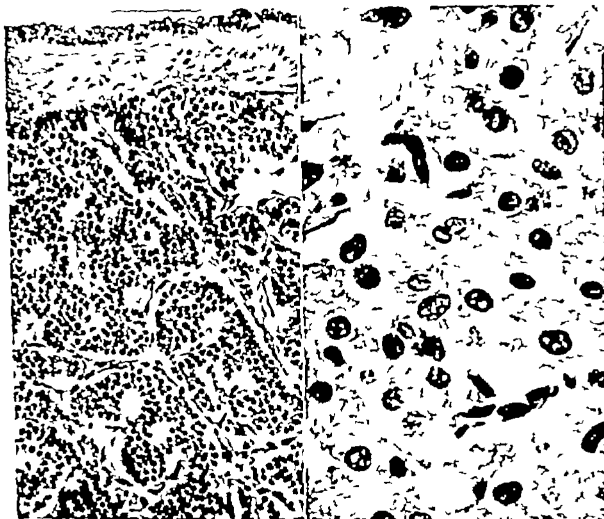


Fig 204—Photomicrograph of so-called bronchial adenoma with a carcinoid pattern and intact overlying epithelium. (Low power) (W U neg 49-658)

Fig 205—Photomicrograph of so-called bronchial adenoma with large cells eosinophilic cytoplasm, small nucleus and no mitotic figures (oncocyte type) (×400) (W U neg 48 3779)

The microscopic pattern is variable with multiple sections (Holley), and individual patterns may vary from field to field. In some zones the cells have the appearance of a so-called oncocyte with well-defined cytoplasmic outlines, voluminous pink cytoplasm, and a small nucleus with fine nucleoli (Fig 205) In other areas the cytoplasm is diminished and pale and the nuclei are small and uniform with fine nucleoli When the tumor has this pattern it is often designated as the

carcinoid type (Fig 204) Mitotic figures are rare. Attempts at demonstrating silver granules have been almost uniformly unsuccessful except for Hamperl's study In still other areas the process may have an adenomatoid pattern. Usually there is no mucin present within the cells, but rarely small amounts may be found. When this tumor invades bronchial cartilage, fragments of the cartilage may undergo metaplasia to bone islands of cartilage and bone may become separated and appear within the tumor, but these islands are not an integral part of the tumor This tumor should be designated as a carcinoma, Grade I but rigidly separated from the usual carcinoma of the lung when reporting end results on patients treated by lobectomy and pneumonectomy The carcinoid type of bronchial adenoma has always been thought to resemble the carcinoid tumors of the small bowel but there has always been some doubt as to whether they have the same histogenesis It has now been shown that a carcinoid tumor of the small bowel may produce the hyperserotonin syndrome after metastasis to the liver has developed Stanford reported a bronchial tumor of the carcinoid type that metastasized to the liver and caused this syndrome. This was further substantiated by the positive urine test for serotonin metabolite 5-HIAA This seems to be excellent objective proof that the histogenesis of these two tumors must be closely related if not similar

Clinicopathologic Correlation—These tumors occur in major bronchi, and because of their vascularization there is a strong tendency to repeated hemoptysis. With either partial or complete blockage of the bronchi, pulmonary infection dominates the clinical picture. These tumors cannot be removed completely by morselization through the bronchoscope. If the tumor is so located that lobectomy is possible, this should be done. If the tumor is so located that complete removal is impossible by lobectomy or if there are secondary inflammatory changes in the rest of the lung as to make it nonfunctioning then pneumonectomy must be resorted to Distant metastases from this tumor are rare but have been reported by numerous observers (Anderson Geever)

Adenocarcinoma, Cylindromatous Type.—A tumor arising from the mucous glands of the bronchus is often classified as a common bronchial adenoma of cylindromatous type This neoplasm should be separated, however for it has a much worse prognosis We had 53 bronchial adenomas with 3 of the cylindromatous type. Moersch had 9 cases of cylindromatous type in 86 adenomas. This lesion arises in the major bronchi, frequently invading the trachea (McDonald) Metastasis to regional lymph nodes is common, and there is often involvement of the lung with distant metastases (Fig 206) Microscopically the tumor is a mucin secreting adenocarcinoma and conforms in pattern with the same type of tumor described under Salivary Glands. Usually it is well differentiated (Fig 207) If this tumor is diagnosed on bronchoscopic biopsy pneumonectomy is the treatment of choice. Irradiation therapy may be helpful. Often the total duration of the disease is long

Bronchiolar (Alveolar Cell) Tumors.—The bronchiolar (alveolar cell) tumor has two distinct gross patterns. It may form multiple nodules in both lungs or a single poorly delimited mass within a lobe. Only the latter form is a surgical





Fig 206—Gross photograph of extensive involvement of the lung bronchi and regional lymph nodes of an adenocarcinoma arising from the mucous glands (cylindromatous type) (W U neg 48-5015)

Fig 207—Photomicrograph of tumor shown in Fig 206 demonstrating its well-differentiated character and origin from mucus-secreting glands. (Moderate enlargement) (W U neg 49-108)

Fig 208.—Typical roentgenogram of a bronchiolar (alveolar cell) tumor Note poorly defined shadow in right lower lung field. (W U neg 48-4750)

Fig 209—Typical gross appearance of a bronchiolar (alveolar cell) tumor It has a mucoid surface looks somewhat like organizing pneumonia, and has poorly defined borders. (W U neg 50-3577)



Fig 210—Photomicrograph of a typical well-differentiated bronchiolar (alveolar cell) tumor Note papillary character absence of cilia and uniform pattern. (High power) (W U neg 48-5631)

problem. Because there is no lesion within the main bronchi, the process may suggest an organizing pneumonia (Figs 208 and 209) The mass may have a mucoid surface Usually the surgeon is not aware that the lesion is a neoplasm Microscopically the tumor forms well-differentiated papillary masses with tall columnar cells which contain epithelial mucin and are rarely ciliated (Swan) (Fig 210) Tumor nodules have a topographic association with bronchioles and not with bronchi. Continuity between tumor cells lining alveoli and the epithelium of respiratory bronchioles or alveolar ducts can be demonstrated (Laipply) Inflammatory cells and fat filled macrophages are frequently associated with the tumor

The histogenesis of this tumor is debatable but there is strong evidence that it arises from terminal bronchiolar epithelium (Herbut) and grows out to invest the alveolar wall As this lesion may have multiple foci of origin and may have a long clinical duration (Delarue) lobectomy rather than pneumonectomy appears to be the treatment of choice. Lobectomy would be done to relieve complicating inflammation rather than with the hope of removing all the neoplasm. Metastatic adenocarcinoma may be erroneously diagnosed as a primary alveolar cell tumor The entity pulmonary adenomatosis we believe shades imperceptibly into a malignant (alveolar cell) tumor

Carcinoma.—Carcinoma of the lung has become increasingly frequent during the past fifteen years This is apparently due not only to increased recognition and better radiologic and bronchoscopic diagnoses, but also to a true increase in incidence (Steiner) In some hospitals such as the veterans hospitals or where thoracic surgery is a prominent specialty carcinoma of the lung is the most frequent neoplasm This increase is almost entirely in males with epidermoid carcinoma of the bronchus. There has been much speculation as to the cause of this increase. Many factors previously considered of etiologic importance can now be eliminated (tuberculosis, tarring of roads, the influenza epidemic of 1918 anthracosis, and anthrasilicosis) There appears to be little doubt that exposure to chromates (Machle) asbestosis (Lynch), and to radioactivity in certain mines (Sikl) accounts for a small fraction of this increase. Tobacco smoking particularly cigarettes, has been found to be an etiologic factor in cancer of the lung Male smokers living in an urban area have a higher incidence of lung cancer than those living in a rural area (Mills) This suggests that air pollution potentiates the carcinogenic action of tobacco in susceptible males Auerbach's meticulous histologic observations on the tracheobronchial trees of 117 autopsies support the etiologic relationship of heavy cigarette smoking to cancer of the bronchus. "Although definite carcinoma in situ was present in all groups, with a parallel rise in proportion to increasing cigarette consumption there was an almost similar distribution of this change in those who smoked more than one package a day (6 0 per cent) and in the cases of bronchogenic carcinoma (6.3 per cent)" (Auerbach)

The *epidermoid carcinomas* of the lung appear almost entirely in males *adenocarcinomas* are about equally divided between males and females. The gross pattern of these tumors depends on their localization. If they arise centrally in a large bronchus, then early block with distal inflammation occurs. In these cases the tumor may form a polypoid mass within the lumen of the bronchus, or may



Fig 211.—Gross photograph of a carcinoma of the lung growing mainly intrabronchially Note peripheral atelectasis. (W U neg 48-4633)

Fig 212.—Gross photograph of the same tumor shown in Fig. 211 demonstrating its gross characteristics. (W U neg 48-4600)



Fig 213—Gross photograph of a large squamous carcinoma of the bronchus which has narrowed the lumen, ulcerated the surface destroyed the wall and extended out into the parenchyma (W U neg 48-5197)

show only a granular appearance (Figs. 211 and 212) The tumor gradually replaces the lumen, destroys the wall and blocks the bronchus (Fig 213) The squamous carcinomas are granular they usually are undifferentiated, yellowish gray lesions. If they secrete mucin they have a mucoid glary appearance. If situated peripherally, they may cavitate centrally leaving a rim of tumor about a central area of necrosis. A lung tumor can arise in the apex of the lung grow out to involve the pleura, and destroy adjoining bone and muscle. Such lesions are sometimes called superior sulcus tumors.

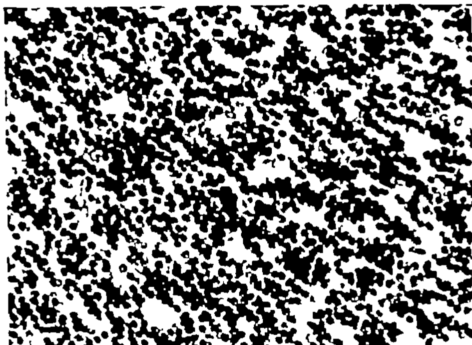
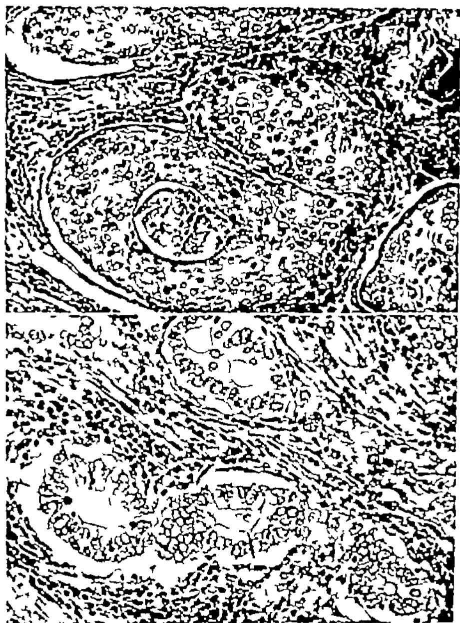


Fig. 214 —Photomicrograph of an undifferentiated carcinoma of the bronchus of the small cell type. This variant of bronchogenic carcinoma is practically never curable. (×300) (W U neg 48-6218)

Surgical resection is not indicated when there is too wide local spread of the cancer Clinical findings which contraindicate attempted resection are involvement of the ribs when their resection is not feasible and tumor cells in pleural fluid. Paralysis of a vocal cord indicates an incurable lesion but resection may be feasible in selected cases for palliation The local extent of the tumor is often not recognized at bronchoscopy or by x ray examination so that a locally far advanced process may be found at the time of exploratory thoracotomy making removal impossible.

Epidermoid carcinoma of the bronchus often is accompanied by squamous metaplasia and frequently by epidermoid carcinoma in situ (Black) We have had instances in which epidermoid carcinoma in situ spread along the bronchus several centimeters from the primary tumor (Fig 199) We have observed the appearance of a second primary carcinoma in the opposite bronchus six years after pneumonectomy for cancer and the presence of carcinoma in situ in the remaining bronchus after pneumonectomy Squamous carcinomas are usually poorly differentiated but cases showing prominent keratinization with slow growth have been

reported (Goldman) A few squamous carcinomas if stained for mucin show cytoplasmic mucin Intermingling of squamous carcinoma and adenocarcinoma is not common The adenocarcinoma forms well-defined mucin producing glands which are not ciliated The degree of differentiation varies. When this tumor



Figs. 215 and 216.—Photomicrographs of carcinoma of the lung which showed both squamous carcinoma, Fig 215 and adenocarcinoma, Fig 216 (×300) (Fig 21 [illegible] U neg 50-5216 Fig 216 W U neg 50-5215)

occurs peripherally it is almost impos [illegible] nine whether it is metastatic unless there is a definite br [illegible] The undiff[illegible] cell tumors (oat cell tumors) usually [illegible] at bron[illegible] only rarely operable The individual [illegible] larger cytes, stain densely and contain little c[illegible]) (Fig

is also a form of carcinoma which shows remarkable pleomorphism with many tumor giant cells. Rarely minute lesions in the lung may be interpreted as early carcinoma or possibly as bronchial adenoma (Fig 192) These lesions have been discovered accidentally or in association with cystic disease (Womack) We have seen multiple such lesions in cystic disease associated with a carcinoma In the periphery of the lung the carcinomas are more often adenocarcinomas, this area is where mixtures of adenocarcinoma and squamous carcinoma are most common (Figs 215 and 216)

Clinicopathologic Correlation.—The early symptoms and signs of bronchogenic carcinoma are related to partial or complete block of a bronchus The symptoms



Fig 217.—Photomicrograph of vein invasion. The tumor is outlined by the blackened elastic tissue of the vein wall (×210) (W U neg 49 1839)

produced are usually those of an inflammatory condition. The radiographic picture changes with variation in the degree of bronchial block Unfortunately the symptoms and x ray findings may be erroneously interpreted as a virus pneumonia tuberculosis, or some other inflammatory process. In the periphery of the lung the lesion is silent until it reaches a sufficient size to ulcerate into a bronchus or involve the pleural surface. Of every 100 patients who come to the Thoracic Surgery Clinic at Barnes Hospital only about 50 can be explored and only 25 have a pneumonectomy with hope of cure Routine chest surveys of asymptomatic individuals occasionally show lesions which are carcinoma. Hood reported 156 solitary circumscribed lesions of the lung one out of three lesions proved to be malignant tumor Calcification was not present in a single malignant lesion Forty

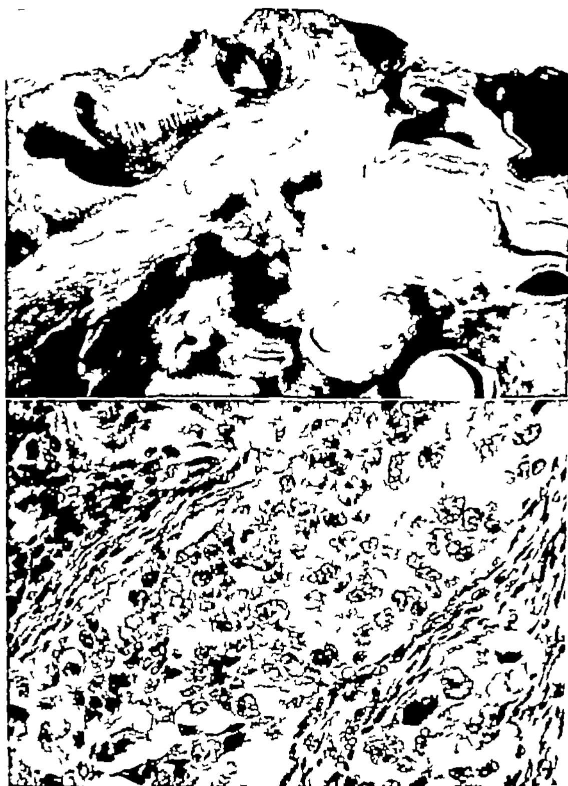


Fig 218 —Gross photograph of epidermoid carcinoma of the lung resected by Dr Evarts Graham in 1933 Note extension into the surrounding lung to involve two regional lymph nodes. The patient is still living and well in 1958 (W U neg 48-5900)

Fig 219 —Photomicrograph of the undifferentiated squamous carcinoma shown in Fig 218 (High power) (W U neg 48-6220)

two per cent of the noncalcified ones were malignant Early exploratory thoracotomy of these patients will increase the number of cases suitable for resection If the tumor has extended to involve a rib, the recurrent laryngeal nerve, or the pericardium or has extensively implicated hilar lymph nodes, cure is practically impossible even by the most aggressive surgical procedure Epidermoid carcinoma has the best prognosis. Collier has stressed the prognostic value of true vein invasion (Fig 217) In a report of 226 patients who had pulmonary resections for cancer he found that with vein invasion only 6 per cent survived five years if lymph node involvement was present without vein invasion 60 per cent survived five years and, finally, if neither lymph node nor vein involvement was present 83 per cent survived five years However we have 3 patients out of 38 who survived over five years who had vein invasion The small-cell carcinomas are seldom resectable and practically never curable The so-called bronchial adenoma is curable in most instances (Overholt) Exploratory thoracotomy at the present time has practically no operative mortality Pneumonectomy by experienced thoracic surgeons has a mortality of 5 per cent or less. Gibbon reported 532 consecutive cases of cancer of the lung Of the patients having pneumonectomy or lobectomy 22 per cent survived five years (9 per cent of the entire group) Our results have been comparable between January 1 1948 and December 31, 1955 the Thoracic Surgery Service at Barnes Hospital saw 1,008 patients with carcinoma of the lung, 390 were inoperable and 15 refused operation. Of 603 exploratory thoracotomies, the tumor was resected in 356 There were 280 pneumonectomies 74 lobectomies, and 2 segmental resections. There were 482 patients on whom a five year follow up was possible of these, 38 were cured (an over all salvage of 8 per cent, or 21.3 per cent of the resected cases) (Burford) The first patient to have his lung successfully resected for an epidermoid carcinoma by Dr Evarts Graham in 1933 is still surviving in 1958—an eloquent witness of the curability of carcinoma of the lung (Figs. 218 and 219)

Rare Tumors Benign and Malignant.—Rare benign tumors of the bronchus include *lipoma* (Fig 220), *neurofibroma leiomyoma* and *granular cell myoblastoma* We have also seen one instance of a polypoid nonneoplastic *inflammatory polyp* completely blocking a bronchus. *Fibrosarcoma* (Black) *leiomyosarcoma* and *carcinosarcoma* (Bergmann) are rare malignant tumors of the bronchus which often present as polypoid neoplasms. With carcinosarcoma the biopsy may show one or both elements. These neoplasms grow rather slowly, and their presence is an indication for resection In one case pneumonectomy for fibrosarcoma was followed by five years without symptoms only to have local recurrence cause death by invasion of the pericardium We have 2 patients with carcinosarcoma who have now survived over five years following pneumonectomy (Figs. 221 and 222) Also observed have been a *neurofibroma* growing between the fissures of the lung several *hemangiomas* of lung parenchyma, two benign *leiomyomas* occurring beneath the pleural surface, and 2 *primary lymphosarcomas* of the lung which were resected with good results Lymphosarcoma if primary in the lung has a better prognosis than does bronchogenic cancer (Fig 223) (Rose) We have also observed a large nonneoplastic polypoid fibrous mass obstructing a peripheral bronchus. Umiker reported 4 *pseudotumors* of the lung we have seen 2 similar cases.



Fig. 220.—Gross photograph of a large lipoma involving the bronchus. It had a bright yellow color. (W. U. neg. 51-1695.)

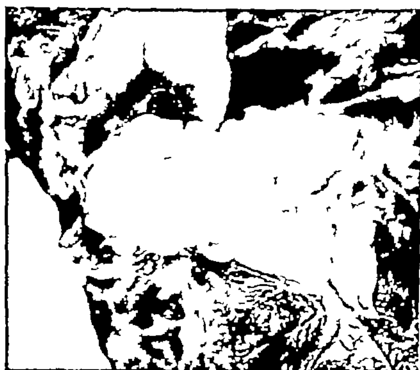


Fig. 221.—Gross photograph of a polypoid carcinosarcoma of the bronchus. This patient has now survived over five years. (W. U. neg. 49-1939.)

Fig 222.—Photomicrograph of carcinosarcoma showing rather sharp demarcation between the squamous carcinoma and the sarcoma. (×460) (W U neg 50-5417)



Fig 223.—Gross photograph of a homogenous localized lymphosarcoma occurring in the left upper lobe in a 74-year-old woman. Pneumonectomy was done by Dr Evarts Graham, and the patient died five years later without evidence of disease. (W U neg 48-7010)

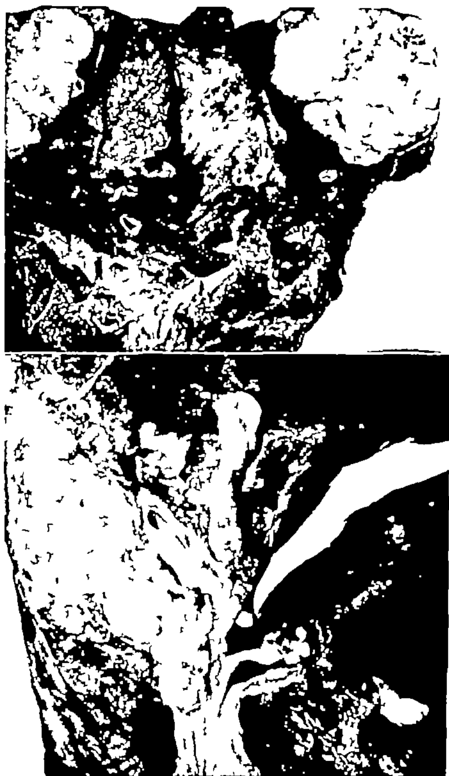


Fig 224 —Gross photograph of well-defined chondrosarcoma metastatic to the lung in a patient who had had this type of tumor in the tibia several years before. (W U neg 49-1757)

Fig 225 —Gross photograph of a carcinoma of the rectum which has secondarily involved the bronchus to form a polypoid mass—a rare occurrence (W U neg 51-857)

These lesions were circumscribed, and microscopically were made up of very cellular fibrous areas. The question was whether these lesions were fibrosarcomas. However foam cells with sudanophilic material plasma cells and lack of mitotic activity were sufficient basis to rule out a malignant neoplasm

Metastatic Tumors.—Metastatic tumors of all types grow freely in the lung parenchyma. These metastases may be single or restricted to a single lobe of the lung and thereby be curable by resection. Seiler recently reviewed the literature and found 62 cases including 10 of his own from the Mayo Clinic. Resection for carcinoma was done in 39 patients of whom 13 are living and for sarcoma in 18 patients, of whom 10 are living. The most common metastatic carcinomas were from the large bowel (11) kidney (7) and ovary (5). There were also 7 metastatic fibrosarcomas. Generally, the neoplasms most favorable for resection are well-differentiated sarcomas (Fig 224) we have resected well-differentiated fibrosarcomas and leiomyosarcomas. The resectable tumors do not usually cause any pulmonary symptoms and are picked up by properly spaced roentgenograms of the chest. Infrequently metastatic cancer involves hilar lymph nodes or lung and extends secondarily into the bronchus. We have seen this occur in testicular tumors, carcinoma of the kidney and carcinoma of the rectum (Fig 225). Certain neoplasms grow so rapidly and produce such diffuse pulmonary involvement that attempted resection is not indicated. Among these are carcinoma of the stomach, testis, malignant bone neoplasms and carcinoma of the breast.

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Chapter 6

MEDIASTINUM

INTRODUCTION

The mediastinum contains many organs and structures from which various types of cysts and neoplasms may arise. At present, thoracic surgery has advanced so far in technique and safety that exploratory thoracotomy can be performed with little risk. For instance, Blades reported a series of 109 cases treated at Army Thoracic Surgery Centers with no operative mortality Therefore the nature of these neoplasms has assumed great practical significance. The pathologist has been forced by the advances in thoracic surgery to differentiate and classify them more accurately If a mass is seen on roentgenographic examination it is far better to explore the mediastinum than to give a so-called test dose of irradiation, for it may be a resectable neoplasm or perhaps only a cyst. Large anterior mediastinal tumors have been successfully identified by needle biopsy This has included such tumors as thymomas, substernal thyroids and malignant neoplasms. Because of faulty embryogenesis thyroid tissue may be present in the mediastinum usually in the superior or anterior portion we have seen it just above the diaphragm in the posterior mediastinum (see Thyroid) Parathyroid tissue also may be intramediastinal (see Parathyroid) Tumors secondarily invading the mediastinum from the esophagus, lung parenchyma, bronchus, pleura, chest wall

or vertebra may be confused with primary mediastinal neoplasms, but these will not be discussed here.

The variety of lesions seen in the mediastinum has been tabulated by Schlumberger who arranged them according to his concept of incidence and site of relative frequency (Table 7). Many of the lesions listed are rare.

TABLE 7 LOCATION OF TUMORS AND CYSTS IN THE MEDIASTINUM*

ANTERIOR MEDIASTINUM	SUPERIOR MEDIASTINUM	MIDDLE MEDIASTINUM	POSTERIOR MEDIASTINUM
Thymoma	Goiter	Bronchogenic cyst	Neurilemoma
Teratoma	Bronchogenic cyst	Lymphoma	Neurofibroma
Goiter	Parathyroid adenoma	Pericardial cyst	Ganglioneuroma
Parathyroid adenoma	Myxoma	Plasma cell myeloma	Sympathicoblastoma
Lymphoma	Lymphoma		Fibrosarcoma
Lipoma			Lymphoma
Fibroma			Goiter
Lymphangioma			Xanthofibroma
Hemangioma			Gastroenteric cyst
Chondroma			Chondroma
Thymic cyst			Myxoma
Rhabdomyosarcoma			Meningocele
			Paraganglioma

*From Schlumberger H G : Tumors of the Mediastinum Atlas of Tumor Pathology Section V Fascicle 18 Washington, D C 1951 Armed Forces Institute of Pathology

NONNEOPLASTIC CYSTS

Pericardial Cysts (Coelomic)

Pericardial cysts arise as failures in embryonic development (Lambert) The pericardium is formed by the fusion of multiple disconnected lacunae. Failure of one of the lacunar cavities to merge with the others may result in the development of a pericardial coelomic cyst. These cysts commonly occur in the cardiophrenic angle (Lillie) They are soft and unilocular and are usually adherent to the pericardium by an easily separated band (Fig 226) At times multiple cysts may be present (Maier) they contain clear fluid unless infected These lesions may be strongly suspected but cannot be accurately diagnosed without exploration We have seen one case in which radiographically the configuration suggested metastatic carcinoma. Their blood supply comes from the pericardium The wall shows a thin layer of mesothelium.

Tracheal, Bronchial, Esophageal, Gastroenteric, and Gastric Cysts

Laipply s explanation of the development of these cysts appears well supported. In the embryonic stage the fusion of the lateral walls which form the tracheal-esophageal septum begins caudally At this time, if a small bud or diverticulum of the foregut is pinched off this bud might be carried into the mediastinum by the downward growth of lungs. The diverticulum would contain entoderm and mesoderm which were destined to become part of the trachea, bronchi esophagus stomach or intestine. This theory is a good explanation for the formation of bronchial espohageal gastric, and enteric cysts of the mediastinum (Laipply)

Bronchial cysts occur along the tracheobronchial tree but are most common in the superior mediastinum either anterior or posterior to the tracheal bifurcation. Rarely they can occur just above the diaphragm. They do not communicate with the tracheobronchial tree. These cysts contain clear or gelatinous fluid and do not reach a large size (Fig 227) Microscopically they are usually lined by ciliated columnar epithelium (Fig 228) The wall may contain hyaline cartilage, smooth muscle, and nerve trunks Because of variation in location they may cause early symptoms or be an entirely incidental finding



Fig 226—Gross photograph of a unilateral thin walled pericardial cyst. (W U neg. 48-3399)

Esophageal cysts are usually not reported as such but as portions of mixed cysts consisting of bronchial and esophageal elements or gastric and esophageal elements. The remaining cysts may consist entirely of gastric elements or intestinal elements or be combined and be designated as *gastroenteric cysts*

Gastric cysts are usually located paravertebrally in the posterior mediastinum behind the trachea and esophagus They are made up of the same coats as the stomach and the enteric group simulates the wall of normal intestine. Nerve fibers and ganglia are often present (Abell)

None of these congenital cysts communicate with the tracheobronchial tree or the esophagus. They are not neoplasms and malignant change does not take place within them. Symptoms from these cysts are related to pressure phenomena and consist of cough dysphagia recurrent pulmonary infection, dyspnea pain and rarely hemoptysis

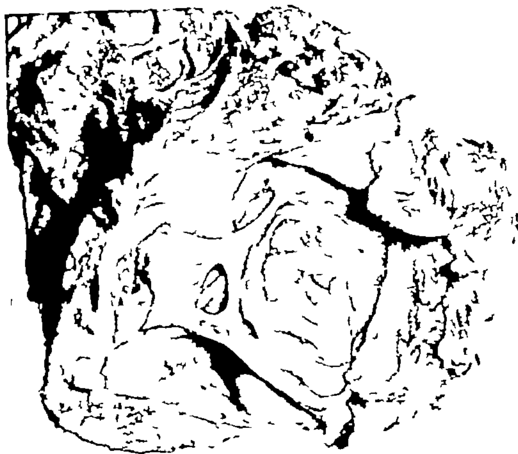




Fig 227 —Gross photograph of the inner surface of a smooth walled large bronchial cyst. (W U neg 48-6734)

Fig 228 —Photomicrograph of the lining of the cyst shown in Fig. 227 The surface epithelium is ciliated and columnar (×240) (W U neg 49-344)

TUMORS

Teratoma

Teratomas usually become clinically apparent in early adult life. Only a small percentage of these neoplasms are malignant They grow to a large size and often have a distinct sharply delineated wall which may become calcified the cystic tumor may become adherent to surrounding structures (Rusby) Calcification may be preesnt within the neoplasm. These tumors sometimes perforate into the tracheobronchial tree and the patient may cough up sebaceous oily material and hair (Fig 229) If the sebaceous material within them escapes, a prominent inflammatory reaction results Microscopically these teratomas resemble those of the ovary They are lined by stratified squamous epithelium and contain abundant sebaceous glands (Fig 230) Hair is invariably present. The more tissue sections made, the more types of tissue revealed. It is common to find skin intestine, bronchus bone cartilage, and nerve tissue (Fig 231) Pancreatic tissue strangely enough is also quite frequent (Schlumberger)



Fig 229—Gross photograph of a large benign cystic teratoma of the anterior mediastinum. Hair can be seen clearly (W U neg 48-899)

Malignant teratomas make up only a small fraction (less than 5 per cent) of all mediastinal teratomas Although they grow more rapidly some malignant teratomas cannot be distinguished from their benign counterparts at the time of roentgenographic or gross examination In others rapid infiltrative growth and local and distant metastases make their malignant nature evident. Malignant teratomas may show increased cellularity frequently areas of hemorrhage and necrosis are



Fig. 230.—Photomicrograph of the usual lining of a teratoma. There are stratified squamous epithelium and abundant sebaceous glands. (Low power.) (W. U. neg. 49 256.)

Fig. 231.—Photomicrograph of epithelium suggesting large bowel in a benign teratoma. (×200.) (W. U. neg. 49 253.)

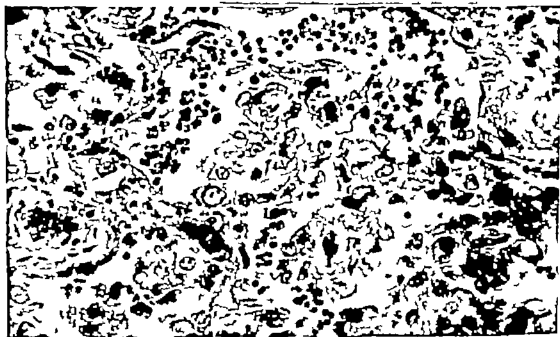


Fig 232.—Gross photograph of a malignant teratoma of the mediastinum which was highly cellular but still encapsulated. (W U neg 48-5292)

Fig 233 —Photomicrograph of malignant teratoma. Tumor cells are poorly differentiated. (High power) (W U neg 49 588A.)

present (Fig 232) Microscopically the tumor may be an undifferentiated squamous carcinoma or a mixture of carcinoma and sarcoma in which elements of a teratoma are seen (Fig 233)

Primary choriocarcinomas of the mediastinum are rare. Most of them probably represent metastases from an occult malignant tumor of the testis. In order to prove that the choriocarcinoma of the mediastinum is primary it is theoretically necessary to section both testes serially (Laipply) Some observers even believe that a small scar found in a testis may be evidence of a previously existing choriocarcinoma (Symeonidis) We have seen a male patient with a mass in the anterior mediastinum which continued to enlarge despite irradiation therapy It was noted at that time by clinicians that both breasts were prominent Friedman's test was positive Both testes were normal to palpation The patient soon died of distant metastases but we do not know whether a primary tumor of the testes existed because permission for autopsy could not be obtained

Thymic Neoplasms

Thymic cysts can occur both in the mediastinum and in the cervical region and are derived from a remnant of the third branchial pouch Such a cyst is usually seen as an anterior mediastinal mass or as a palpable mass above the suprasternal notch (Krech) A rare lesion found usually in children may form a tumor mass made up of thymic and adipose tissue (Rubin) In our experience the mysterious group of thymic neoplasms are the commonest tumors of the anterior mediastinum

In *myasthenia gravis* about 15 per cent of the cases show a benign encapsulated neoplasm These tumors vary in their epithelial and lymphocytic components. With prominent epithelial elements an incorrect diagnosis of carcinoma may be made (Fig 234) The thymus usually shows lymphoid germinal centers and their presence in large numbers according to Castleman almost certainly means myasthenia gravis. Germinal centers are not present in the normal thymus. As Iverson has emphasized spindle shaped cells are exhausted cells and the large ovoid cell with a plump nucleus represents a functionally active gland often associated with myasthenia gravis.

The transition between hyperplasia and adenoma is difficult to describe. Adenomas may be implanted but malignant change in them has not been reported. The lesions do not usually occur in the absence of myasthenia gravis (Castleman) If epithelial elements predominate in a benign tumor of the thymus this microscopic finding indicates the presence of myasthenia gravis in at least 70 per cent of the cases In 2 patients cited by Castleman such epithelial elements predominated without clinical myasthenia gravis. Later both patients developed classic myasthenia gravis Effler has reported myasthenia gravis in association with malignant thymic neoplasms Bayrd has collected 12 instances of benign thymomas with agenesis of erythrocytes One of our patients had agammaglobulinemia, severe leukopenia and splenomegaly (Ramos) The cause of such an association is unknown.

We have seen several large *thymomas* which have had characteristic lobulated shadows in the anterior mediastinum (Figs. 235 and 236) These tumors are

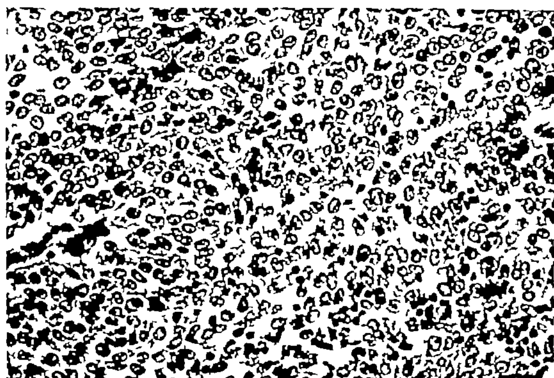


Fig 234.—Photomicrograph of an adenoma in a patient with myasthenia gravis. Epithelial elements predominate in patients with myasthenia gravis and associated thymic tumor. Approximately 15 per cent of patients with myasthenia gravis have such benign adenomas. (×400.) (W U neg 52 3449.)

Figs. 235 and 236.—Roentgenograms of a lobulated large benign thymoma located in the anterior mediastinum. (Fig 235 W U neg 49-3479; Fig 236 W U neg 49-3480.)

large with a well defined capsule, yellow in color without necrosis and contain fibrous connective tissue septa (Fig 237) Microscopically they are made up of prominent lymphoid tissue, often there are rather large cells with well-defined nuclei. Connective tissue stroma is variable, and definite Hassall's corpuscles are usually absent (Fig 238) Surgical removal of these large tumors is curative.

We have also seen rare examples of the so-called *granulomatous type thymoma* which microscopically simulates Hodgkin's disease (Lowenhaupt) However, we now believe that in most if not all cases the diagnosis of Hodgkin's disease is the correct one. In reality a granulomatous type of thymoma does not exist. Iverson has separated from the group of thymomas lesions resembling seminomas. The *malignant thymoma* may be extremely vascular and have areas of calcification It tends to implant and extend into the lung rather than to metastasize distally (Fig 239) Usually it is difficult to recognize their thymic origin The so-called oat-cell carcinoma of the lung and lymphosarcoma of mediastinal lymph nodes are often confused with a primary malignant tumor of the thymus (Seybold) The location of the neoplasm its pattern of growth and the microscopic picture must be considered in making a diagnosis of malignant thymoma (Fig 240) Some malignant tumors may appear well differentiated, and the diagnosis of their malignant nature depends more on their behavior than on their microscopic pattern

Castleman has emphasized localized lymph node hyperplasia resembling thymomas. Such lesions are made up of very large masses of lymph nodes, sometimes reaching a diameter of 12 cm. and a weight of 100 grams. The germinal center changes are often misinterpreted as Hassall's corpuscles (Fig 241)

Neurogenous Tumors

The neurogenous tumors of the mediastinum can be classified as follows

- A Tumors of the sympathetic nervous system
  - 1 Ganglioneuroma (well differentiated)
  - 2 Ganglioneuroblastoma (moderately well differentiated)
  - 3 Neuroblastoma (poorly differentiated)
- B Tumors of nerve sheath origin
  - 1 Neurilemoma
  - 2 Ancient neurilemoma
  - 3 Neurofibroma
  - 4 Malignant schwannoma (neurofibrosarcoma)

Tumors of the Sympathetic Nervous System.—The tumors of the sympathetic nervous system show variable degrees of differentiation. A sharp division into the different types cannot be made because one type often blends into another Different degrees of differentiation may occur in the same tumor It is, therefore important to make multiple sections of these tumors With exceptions, the better differentiated tumors occur in older persons while the neuroblastomas occur with higher frequency in children (Blacklock) The undifferentiated tumor is usually nonencapsulated appears high in the mediastinum and infiltrates surrounding tissue. With better differentiation encapsulation takes place, and the tumor may have a lobulated appearance (Fig 242) Areas of calcification possibly secondary to regressive changes are common The well-differentiated *ganglioneuroma*

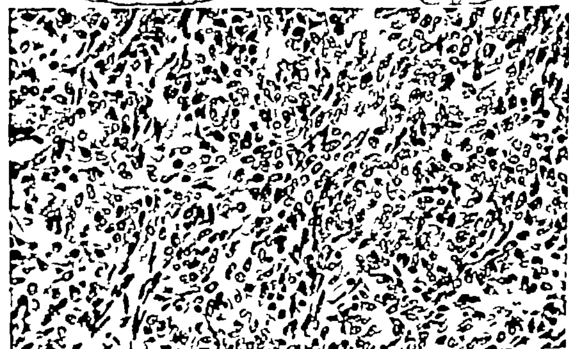


Fig 237 —Gross photograph of large lobulated tumor with encapsulation, no necrosis, and containing connective tissue trabeculae (W U neg 49-3096)

Fig 238.—Photomicrograph of same tumor illustrated in Fig 237 showing spindle-shaped epithelial elements. These changes usually indicate that the patient does not have myasthenia gravis. (400) (W U neg 50-3949)



Fig 239 —Gross photograph of malignant thymoma found in the anterior mediastinum at autopsy There was invasion of surrounding structures but no distant metastases (W U neg 51-4318)

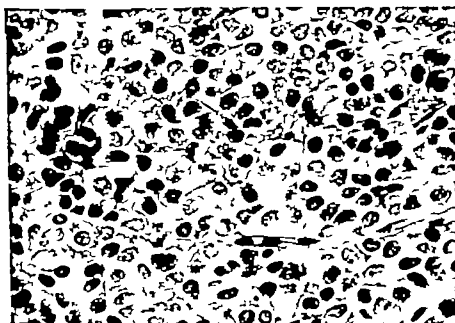


Fig 240 —Photomicrograph of a malignant thymoma. The tumor appears well differentiated, yet there were tumor implants and blood vessel invasion. (×200) (W U neg 52 112.)



Fig 241 —Prominent hilar mass was suspected radiographically of being tumor (W U neg. 56-3604) At operation there was a firm mass intimately associated with the bronchus, thought to represent neoplasm. (W U neg 55-1278) Microscopically this proved to be hyperplastic fused lymph nodes with prominent hyalinized germinal centers. (×600) (W U neg 58-127)



Fig. 242.—Gross photograph of ganglioneuroblastoma which was encapsulated. (W U neg 49-7106.) (From Ackerman, L. V., and Taylor F H. Cancer 4: 669-691 1951)



Fig. 243 —Gross photograph of a large posterior mediastinal ganglioneuroma. (From Ackerman, L. V and Taylor F H.: Cancer 4: 669-691 1951)

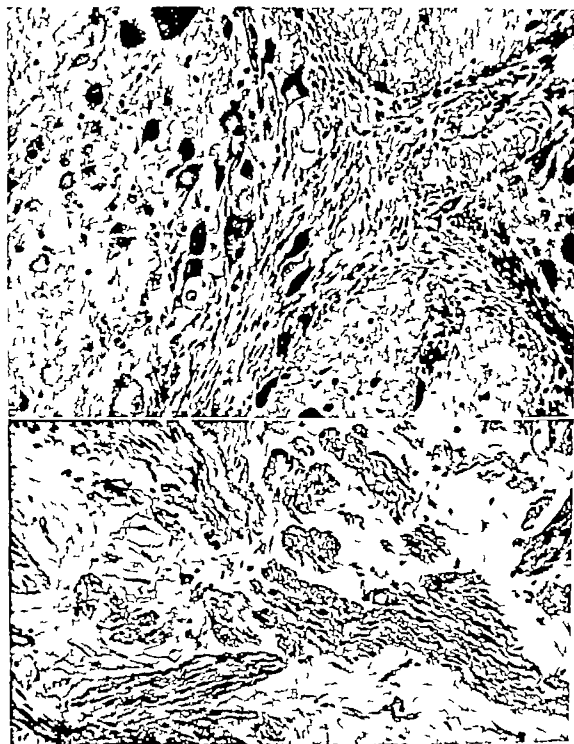


Fig. 244.—Photomicrograph of ganglioneuroblastoma with collections of ganglion cells, schwannian sheath proliferation and cobwebby material. (×200.) (W.U. neg. 50-554.) (From Ackerman, L. V., and Taylor, F. H.: Cancer 4: 669-691, 1951.)

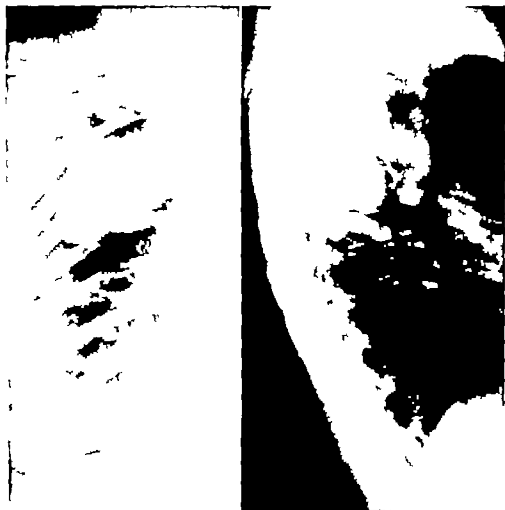
Fig. 245.—Photomicrograph of another area in the same tumor illustrated in Fig. 244 showing prominent schwannian sheath proliferation. (×200.) (W.U. neg. 50-553.) (From Ackerman, L. V., and Taylor, F. H.: Cancer 4: 669-691, 1951.)

forms a smooth well-encapsulated mass, usually in the posterior mediastinum, and on section is often fibrous and yellowish gray in color (Fig 243) It may show areas of cystic change and fatty degeneration necrosis is infrequent. In the undifferentiated *neuroblastoma* the individual cells are slightly larger than the lymphocytes stain deeply, and may show rosette formation with small focal areas of calcification (see Adrenal) With better differentiation the tumor cells become larger the nuclei do not stain so heavily and between the masses of cells there is a cobweb like material which we have not been able to identify It does not stain as glial tissue or as fibroglia fibrils. The presence of this material between masses of tumor cells is often diagnostic. In the better differentiated tumors broad masses of bundles suggesting schwannian sheath proliferation are observed With still further differentiation islands of ganglion cells often twenty or thirty at a time are observed (Fig 244) These ganglion cells may have several nuclei Often associated with these cells are large masses of non myelinated sheaths which are more numerous than might be expected from the number of ganglion cells present (Stout) (Fig 245)

The prognosis of this group of tumors is directly related to their differentiation all ganglioneuromas do well Ganglioneuroblastomas containing both elements have a somewhat unpredictable prognosis but it is not rare to cure such cases In seven patients of our group three are apparently cured The prognosis for neuroblastoma is poor, but irradiation therapy has cured such tumors Tumors of the sympathetic nervous system can be multiple and can occur in different locations with different degrees of differentiation (Wahl)

Tumors of Nerve Sheath Origin.—Stout has divided the tumors of nerve sheath origin into two distinct types neurofibromas and neurilemomas Neurofibroma is nonencapsulated having a tangled network showing schwannian sheath proliferation. Special stains show large numbers of neurites This type of tumor may undergo malignant change. The neurilemoma on the other hand is encapsulated and is made up of Antoni type A and type B tissue Antoni type A tissue is composed of bands of cells with their nuclei arranged in parallel order Antoni type B tissue is made up of cystic spaces containing gelatinous like material. Both of these tissues are specific and can be grown in tissue culture (Murray) Neurites are seen only in the compressed capsule. This tumor is nonmalignant apparently the worst it ever does is to recur locally The sharp differentiation described by Stout may not be apparent in tumors of nerve sheath origin in the posterior mediastinum (Figs. 246 and 247) In fact practically all tumors of nerve sheath origin in this region are encapsulated tumors. These tumors grow rather slowly and are often discovered on routine x ray examination. Regressive change within them, such as fatty degeneration, hemorrhage and cystic formation is common (Figs 248 and 249) We have seen several neurilemomas which were completely cystic. Such regressive changes with overgrowth of fibrous tissue make recognition difficult Frequently the cellularity causes them to be incorrectly diagnosed as sarcoma (Fig 250) It was our feeling after a thorough study of the Barnes Hospital cases that a high percentage of them should be classified as neurilemomas (Ackerman) Many of these neurilemomas were ancient," and they were so classified when

regressive changes were prominent. There were a few cases which were clearly neurofibromas. In our group there were four patients with malignant schwannomas apparently arising from pre-existing neurofibromas. Three of these patients had florid von Recklinghausen's disease. When these tumors become malignant, the change may be hardly perceptible microscopically, the only suggestion being some slight increase in cellularity. With outspoken malignant change the tumor cells individually may become bizarre, and it then may be impossible to recognize



Figs. 246 and 247.—Posteroanterior and lateral views of a sharply delimited neurilemoma occurring in the posterior mediastinum. (Fig. 246, W.U. neg. 48-5735; Fig. 247, W.U. neg. 48-5734.)

the malignant tumor as originating from a pre-existing neurofibroma (Figs. 251 and 252). In these instances, the presence of von Recklinghausen's disease, previous biopsy, or the presence of other neurofibromas may suggest the diagnosis.

The prognosis in this group is excellent with the exception of the malignant schwannomas. We had 10 patients with neurilemomas, 11 with ancient neurilemomas, and 10 with neurofibromas; 28 of these patients are still living and well without evidence of disease. Of 4 patients with malignant schwannoma, 3 are dead and the other is living without evidence of tumor.

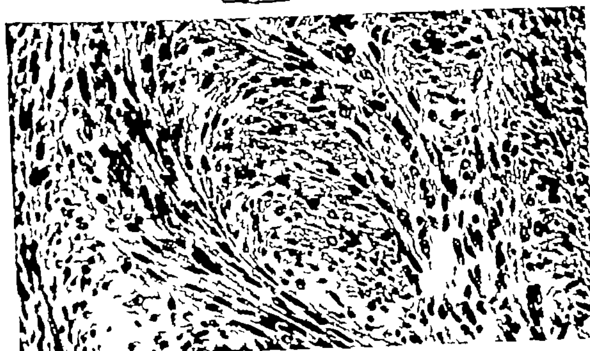


Fig 248 —Gross photograph of same tumor shown in Figs 246 and 247 which is cystic and encapsulated. (W U neg 48-5199)

Fig 249 —Photomicrograph of a cellular area in a neurilemoma with palisading (×330.) (W U neg 49-248)

Malignant Lymphoma

Malignant lymphoma is the commonest tumor of the middle mediastinum. Usually it appears in this area as a secondary manifestation of a disseminated process such as lymphosarcoma or Hodgkin's disease. In a smaller percentage of patients lymphoma first appears in the mediastinum as a conglomerate mass of involved lymph nodes. This diagnosis may be suggested by the radiographic examination, but it cannot be made with certainty without exploratory thoracotomy. In our experience these masses cannot be adequately removed surgically. Only biopsy is feasible, thus, thoracotomy should be performed to establish the diagnosis. These lesions conform microscopically to the various types of malignant lymphoma. We have encountered one plasma cell granuloma in the mediastinum which invaded the lung. The granuloma was associated with amyloid formation. Irradiation therapy of mediastinal lymphoma results in excellent palliation especially in the patients in whom the mediastinum is the initial site of the process. Irradiation reponse should not be used for diagnostic purposes.

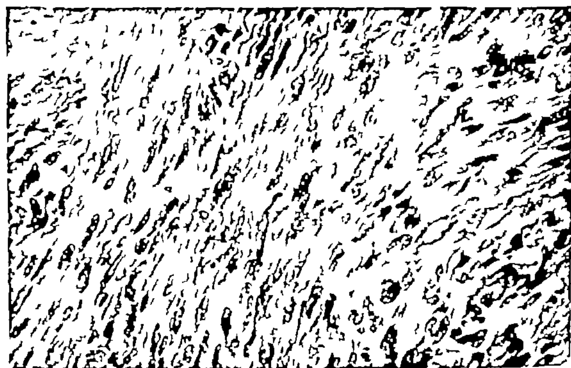


Fig. 250.—Photomicrograph of a highly cellular neurilemoma which was benign but incorrectly diagnosed as malignant because of cellularity. (×600.) (W.U. neg. 50-1594.) (From Ackerman, L. V., and Taylor, F. H.: Cancer 4: 669-691, 1951.)

Metastatic Malignant Tumors

Metastatic malignant tumors are cited only because of their clinical similarity to primary malignant mediastinal tumors. Confusion occurs most commonly when there are metastases to the mediastinum from bronchogenic carcinoma. However many other types of malignant tumors can metastasize to the mediastinum and simulate a primary tumor of this area. We have seen inconspicuous

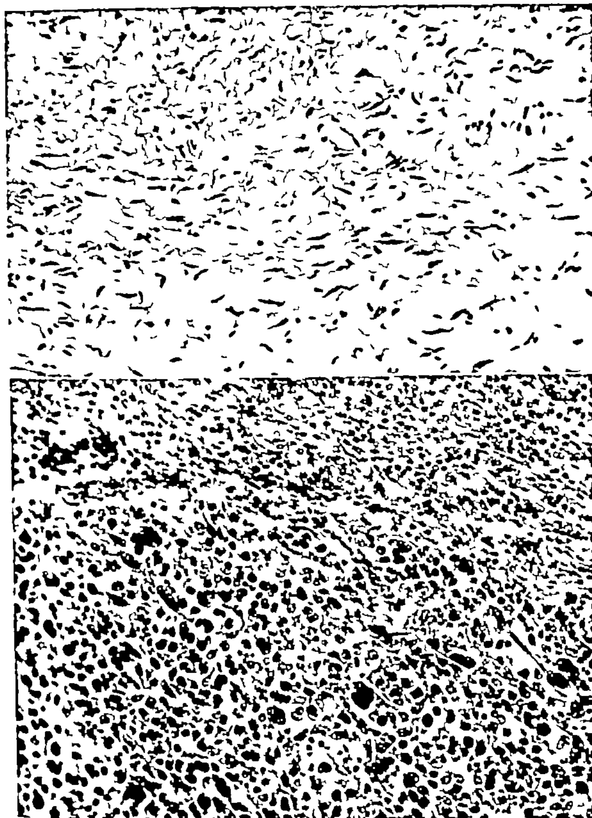


Fig. 251.—Photomicrograph of a malignant schwannoma. Individual cells are quite uniform, and it would be difficult if not impossible to tell that it was malignant. (×200.) (W.U. neg. 50-549.) (From Ackerman, L. V., and Taylor, F. H.: Cancer 4: 669-691, 1951.)

Fig. 252.—Photomicrograph of the same tumor shown in Fig. 251 at a later time period. It shows a highly undifferentiated area with numerous tumor giant cells. (×200.) (W.U. neg. 50-5511.)

...imary carcinomas of the breast and esophagus produce secondary voluminous metastatic masses which mimic a primary mediastinal tumor. Testicular tumors are particularly prone to develop mediastinal metastatic masses.



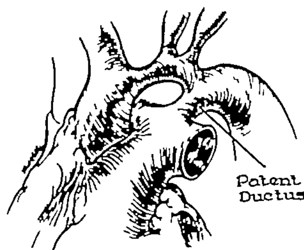
Fig 253.—Roentgenogram showing a lymphangioma of the anterior mediastinum. (W U neg 49-5186.)

Fig 254.—Gross photograph of lymphangioma demonstrating large cystic, smooth-walled spaces. (W U neg 49 5163.)

...are Lesions

Lymphangioma.—Cystic lymphangiomas are rare neoplasms of congenital origin. They may grow large, are multicystic, and are intimately associated with the vessels of surrounding structures (Figs. 253 and 254). Surgical excision is difficult. These lesions can extend into the mediastinum. Microscopically the tumors consist of thin spaces separated by fine septa lined by endothelium. Smooth muscle, lymphoid tissue, and cholesterol crystals may be present. McCorkle describes large mediastinal lipomas. We have seen one liposarcoma primary in the mediastinum. Ringertz has described three tumors of the mediastinum not connected to the bronchus or lung. These tumors had the microscopic pattern of the so-called carcinoid type of bronchial adenoma.

We have seen a number of instances in which a mediastinal mass proved to be made up of a conglomerate group of lymph nodes Microscopically granulomas were present we have seldom been able to prove an etiologic agent (Kunkel)





Figs. 255 and 256—Drawings of the infantile type (diffuse type) and the adult type (localized variant) of coarctation of the aorta. (From Burford, T H S Clin. North America 30: 1249 1258 1950)

CLINICOPATHOLOGIC CORRELATION

It can be seen from this short résumé of the more common lesions that the mediastinum is a veritable Pandora's box. Congenital remnants benign tumors, and primary and metastatic neoplasms occur in it. The location of these lesions in the mediastinum, together with their configuration may give some hint as to the correct diagnosis but many lesions both benign and malignant, give similar radiographic shadows. Exploration is mandatory for all of them its risk is prac

tically zero Cure is effected by excision of the congenital cysts and benign neoplasms. A few patients with malignant tumors may be cured by resection of the tumor

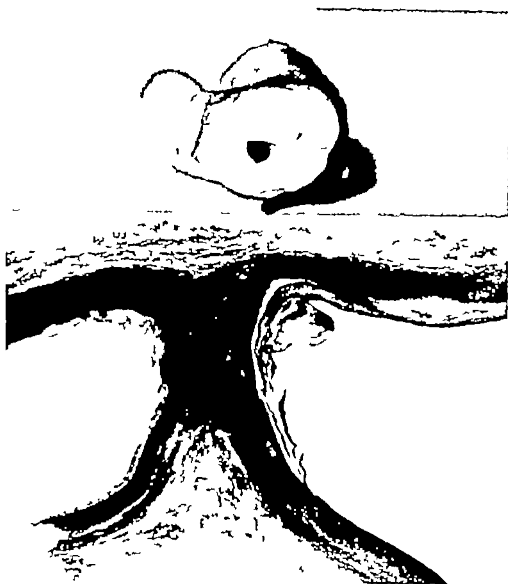


Fig 257 —Coarctation of the aorta of the adult type showing the greatly narrowed lumen. (W U neg 48-5295)

Fig 258 —Photomicrograph of coarctation of the aorta at the point of constriction showing subintimal thickening and medial distortion (Low power) (W U neg 48-6704)

HEART AND AORTA

The heart and aorta used to be considered as outside the province of the surgeon but during the past fifteen years advances in thoracic surgery have fol lowed better understanding of the physiology of the heart and refinement of new procedures in diagnosis and treatment (cardiac catheterization angiocardiography hypothermia, and extracorporeal circulation) Entire books have been written about congenital heart disease (Kjellberg) Most operations for congenital cardiovascular malformations are directed toward improvement in the flow of oxygenated

blood by such procedures as ligation or division of a patent ductus or the Blalock operation the closure of interatrial and interventricular septal defects Methods have been devised to relieve pulmonary aortic, and mitral valvular stenosis In these procedures the surgical pathologist rarely receives tissue. If the operation fails, the cause of failure becomes the concern of the general pathologist. Therefore the various cardiac abnormalities and their methods of treatment will not be presented in detail

Left Auricle in Mitral Stenosis

Mitral valvulotomy may be done for patients with mitral stenosis, and at the time of operation biopsy of the auricular appendage will be done These appendages are always abnormal showing hypertrophy of the muscle and various other alterations About one half of them show actual Aschoff nodules (Clark) We have not been able to correlate the presence of these nodules with the postoperative course nor with clinical evidence of activity of the rheumatic process.

Coarctation of the Aorta

Coarctation of the aorta is usually divided into infantile and adult types but it is probably better to call them diffuse or localized (Hanlon) (Figs. 255 and 256) In the diffuse type the coarctated segment lies proximal to the ductus arteriosus. This type until recently was incompatible with life, but Gross has used homografts to repair the defect In the localized type the short narrowed segment of the aorta is at the level of the aortic insertion of the ductus or just distal to it If resection is not done about 60 per cent of the patients die before 40 years of age (Reifenstein) of aortic rupture endocarditis hypertension or congestive failure. Resection of the segment can be done (Fig 257) Grossly there is concavity of the wall of the vessel except at the point of insertion of the ligamentum arteriosum. On opening the aorta a diaphragm like structure lies across the lumen, through which there is an aperture usually 1 mm or less in diameter (Edwards) Often there is localized subintimal thickening and beneath this the media is distorted and thickened (Fig 258) Operations for coarctation of the aorta are often difficult in older patients because of advanced arteriosclerotic changes in the aorta.

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Chapter 7

PARATHYROID

INTRODUCTION
- Physiology

ADENOMA
CARCINOMA
SECONDARY HYPERPLASIA
PRIMARY HYPERTROPHY AND HYPERPLASIA
EXPLORATORY SURGERY
CLINICOPATHOLOGIC CORRELATION

INTRODUCTION

Normally there are four oval, resilient copper-colored parathyroid glands, each measuring on the average 4 by 3 by 1.5 mm. The number of glands is almost invariably four in number but in rare instances (perhaps 2 to 3 per cent) more are found. The upper pair arises from the fourth branchial cleft and descends with the thyroid during embryonic life to its final position in the neck. The lower pair arises from the third branchial cleft with the thymus and descends with it. Usually its descent ceases at the lower pole of the thyroid, but in perhaps 10 per cent of instances it continues its descent with the thymus into the anterior mediastinum. The color may vary from reddish brown to light tan depending upon fat content, which in turn depends on age, nutrition and activity of the patient. Variations in the size and weight of the normal glands were studied by Gilmour who found that in 189 cases, the mean weight was 117.6 mg plus or minus 4 mg in men and 131.3 mg plus or minus 5.8 mg in women.

Parathyroid glands are arranged in two pairs, the upper pair usually located at the midportion of the posterolateral surface of the thyroid gland and the lower pair on the posterolateral surface of the thyroid near the inferior thyroid artery at the lower pole. It is not at all unusual for parathyroid glands to be in anomalous positions such as the anterior mediastinum where they have been carried by the descent of the thymus, within the substance of the thyroid gland, or even behind the esophagus.

Microscopically there are four major cell types (Fig. 259). The first is the chief or principal cell which is polyhedral and poorly outlined and measures 6 to 8 microns in diameter. Its nucleus is large and round, comprising more than half the cell volume. The cytoplasm is usually scanty and faintly acidophilic and may

be somewhat retracted toward the cell margins, leaving an unstained halo of varying width about the nucleus This is known as vacuolization though it may represent an artefact of fixation The second cell type, the transitional wasserhelle cell is similar to the first except that the halo formation is present in only moderate degree It measures from 7 to 12 microns The vacuoles may be only little larger than those of the chief cells or they may be quite large approaching those of a wasserhelle cell The nucleus is similar to that of the chief cell but with increased size of the vacuole in the cytoplasm it tends to become eccentrically placed. The margins of this cell are poorly defined, and the ability to distinguish it from a chief cell and wasserhelle cell is often a matter of individual experience. Narrow interlacing cords of these two cell types comprise most of the gland parenchyma. The

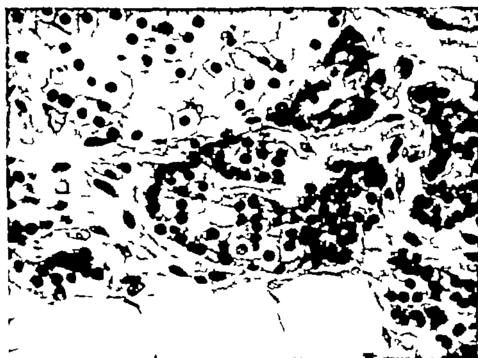


Fig. 259 —Photomicrograph of normal parathyroid. Note lack of encapsulation and persistence of fat. The cells with the deep-staining nuclei are chief cells and those with prominent cytoplasm are oxyphil cells. (×500) (W U neg 49-814)

third type is the wasserhelle cell which is sharply outlined and polyhedral and measures 10 to 15 microns in diameter The nucleus is about the same size as that of a chief cell but is usually more hyperchromatic and eccentrically located. There is complete vacuolization of the cytoplasm. This type of cell is seen only occasionally in the apparently normal gland and then only in small groups. The pale oxyphil cell the fourth type is polyhedral, has a sharply demarcated cell margin and measures 11 to 14 microns in diameter The nucleus is also about the same size as that of the chief cell but not so hyperchromatic. The cytoplasm is uniformly reddish pink and finely granular and completely fills the cell. There is no vacuolization The fifth cell type the dark oxyphil cell is larger than the chief cell but smaller than the pale oxyphil cell measuring 8 to 10 microns in diameter Its cell border is not sharp The nucleus is small 3 to 4 microns, and intensely

pyknotic. The cytoplasm is dark red and homogeneous. This type is probably a degenerating form of the pale oxyphil cell and does not actually deserve a separate classification

The distribution of all of these cells varies with the age of the patient. Until puberty the gland is composed wholly of chief cells with slight tendency to vacuolization These cells contain a fair amount of glycogen but no fat. Fat appears soon after puberty as very fine droplets. At puberty or soon afterward, pale oxyphils gradually appear at first singly and then in pairs increasing in number with advancing age, frequently forming large islands after 40 to 50 years of age. These islands of oxyphil cells are sharply circumscribed but not encapsulated and often continuous cords of parenchymal cells can be traced across the margin of the gland into the surrounding gland. These oxyphil cells do not contain fat or glycogen Single dark oxyphil cells may be seen usually close to the stroma. They are not present before puberty and are usually apparent when pale oxyphils are present. They likewise do not contain fat or glycogen Following puberty, large fat cells appear in the stroma and increase in number until about 40 years of age. The fat tissue remains fairly constant during middle and old age. It is interesting to note that when an adult gland is smaller than normal, the decreased size is due to the absence or marked diminution of fat cells whereas the parenchymal cell volume is about the same as in a normal-sized fat-containing gland. This has been proved by actual measurement by Gilmour Cysts of varying sizes are observed in about one half of the patients beyond puberty These cysts are sometimes filled with granular and cellular debris or with a dark blue-staining finely granular material which has been designated incorrectly as colloid. Rucart has presented evidence that the chief cells may progress through transitional wasserhelle cells to wasserhelle cells and that all of these cells may produce parathormone. Development may also progress toward oxyphil cells which apparently do not produce parathormone.

There are times when it is difficult to make the histologic differentiation between parathyroid and thyroid. Colloid like material in parathyroid tumors and within the thyroid appears to be the same. In the normal parathyroid and in parathyroid tumors there is considerable glycogen. In the normal thyroid there is practically no glycogen. Thyroid nodules and thyroid cancer contain small amounts of glycogen Thus the presence and amount of glycogen observed may be helpful in making a distinction between parathyroid and thyroid (Klinck)

Physiology

The parathyroid glands mediate their endocrine function through the production of parathormone. Some believe that parathormone operates by increasing the quantity of phosphorus excreted by the kidneys because of decreased tubular reabsorption of phosphorus (Albright) Others believe that the primary action of parathormone is that of creating increased solubility of the calcium in the bone. In the case of a functioning parathyroid adenoma Albright demonstrated with bone biopsy that there may be no changes in the bone. However Chang demonstrated that if autogenous and homogenous transplantations of parathyroid gland

were made to the subperiosteal area in the parietal bone in young rats and mice, then there was prominent resorption of parietal bone as well as minimal new bone deposition. These changes strongly suggested a direct local effect. Similar transplants of many other organs such as urinary bladder mucosa, testis, pancreas compact bone etc., caused no changes With a pathologically increased secretion of parathormone, the following sequence of events occurs The decreased reabsorption of phosphate results in increased secretion of phosphorus in the urine—hyperphosphaturia. Accompanying the hyperphosphaturia there is hypophosphatemia. Since an effort is made by the body to keep the product of the calcium ion and the phosphorus ion concentrations constant with the fall of phosphate there is a concomitant rise in the calcium concentration in the serum—hypercalcemia. The increased calcium ion concentration in the blood stream exceeds the kidney threshold for calcium ions, and increased quantities of calcium are excreted—hypercalcinuria. Therefore, the results of increased parathormone secretion are hyperphosphaturia, hypophosphatemia hypercalcemia, and hypercalcinuria. These, then are the four cardinal chemical criteria of hyperparathyroidism. Another associated chemical finding is an elevated serum alkaline phosphatase level when there are bone changes

In Cope's series (1958) of 200 cases of neoplasia in which there was evidence of functioning parathyroid lesion, the distribution was

Neoplasia in the Parathyroid	
Single adenoma	158 cases (79%)
Double adenoma	10 cases (5%)
Carcinoma	8 cases (4%)
Primary Hyperplasia	
Water clear-cell type	14 cases (7%)
Chief-cell type	10 cases (5%)
Total	200 cases

ADENOMA

The term parathyroid adenoma should be confined to a tumor of parathyroid tissue that involves one gland that usually produces symptoms and signs of hyperparathyroidism, that does not metastasize and that may recur if not completely removed. The oxyphil adenoma is considered as a variant, although we have not seen it cause hyperparathyroidism. Recently Sommers reported evidence of hyperparathyroidism in oxyphil adenoma. Adenomas occur in women as compared with men in a ratio of 3 to 1 They can occur at almost any age, but most of them occur in patients in the fourth decade. Adenomas may vary in weight from 0 4 to 120 grams. The mean weight of such tumors reported prior to 1947 was approximately 7 grams. An adenoma of this weight would measure about 3 by 2 by 1.5 cm. Adenomas are usually oval, may show slight lobulation, and usually have a thin connective tissue capsule on section they are commonly grayish brown (Fig 260) Foci of hemorrhage and even calcification may occur Usually only a portion of a gland is involved. Three quarters of adenomas arise in the lower group of glands. Rarely two parathyroid adenomas have occurred (Norris) For instance, Woolner reported six patients with multiple adenomas (4 3 per cent) in 140 patients with tumors and hyperplasia of the parathyroid

glands. Microscopically parathyroid adenomas are made up of any one of a combination of various cell types. Frequently the tumors contain cysts showing a varying amount of colloid like material. Often there is prominent variation in cell size and variation in nuclear size is conspicuous (Figs. 261 and 262) Mitotic figures are rare. We were not able to find any instance of an adenoma composed entirely of oxyphil cells which were functioning (Fig 263) We believe that the chief cell transitional wasserhelle cell, and wasserhelle cell can all produce parathormone (Black)



Fig 260—Gross photograph of a functioning parathyroid adenoma. Note encapsulation and cystic change. (W U neg 46-8655) (From Black B K. and Ackerman L. V Cancer 3: 415-444 1950)

CARCINOMA

Carcinoma of the parathyroid has been too frequently diagnosed in the past, the most common error being made when a malignant tumor in the region of the parathyroid has metastasized Since it does not produce parathormone, such a neoplasm cannot be proved to be of parathyroid origin The microscopic pattern of parathyroid adenomas is exceedingly variable and this variability in size and shape of cells has been used by Alexander as an indication of malignant change. In a study of 23 cases, however we could not see that the cellular changes signified carcinoma nor were the cells of an adenoma trapped in the capsule or seen lying free within the lumina of veins evidence of malignant change. In order for tumor lying in the vein to be of any significance, there must be a true tumor thrombus attached firmly to the wall. The only true evidence of malignant change in a parathyroid adenoma is the presence of invasion of contiguous structures at the time of first operation or the presence of local lymph node or distant metastases. In



Fig. 261.—Photomicrograph of a functioning parathyroid adenoma with extreme variation in nuclear size. This patient is surviving eighteen years following operation. (×500.) (W. U. neg. 49-816.) (From Black, B. K. and Ackerman, L. V.: Cancer 3: 415-444, 1950.)

Fig. 262.—Photomicrograph of a functioning parathyroid adenoma. Note difference in microscopic pattern from adenoma shown in Fig. 261. The patient is surviving after eleven years. (×185.) (W. U. neg. 49-3700.)

Fig. 263.—Photomicrograph of the characteristic cells in an oxyphil adenoma. We have not seen an adenoma of this type which produced parathormone. (×400.) (W. U. neg. 49-3701.)

1954 Black summarized 20 cases of parathyroid cancer reported to date, and there were only 12 with metastases.

The usual carcinoma of the parathyroid has a trabecular pattern with mitotic figures (Castleman) (Figs 264 and 265) In a few instances parathyroid cancer can exactly resemble a benign tumor in both the primary and the metastasis.

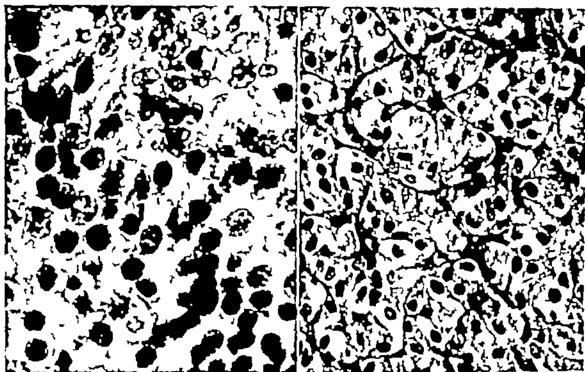


Fig. 264—Photomicrograph of a carcinoma of the parathyroid in which there were nerve invasion tumor thrombi, and numerous mitotic figures Mitotic figures are absent in parathyroid adenomas. (×600) (W U neg 52 158)

Fig 265—Photomicrograph of a carcinoma of the parathyroid. Note the trabecular pattern. This lesion recurred after operation and finally invaded the mediastinum widely (×400) (W U neg 49 3966.)

Bone changes in hyperparathyroidism depend on many factors including the calcium intake, the renal function and the level at which the parathyroid adenoma is functioning With minimal changes the x ray may show simply generalized diminished bone density With advanced changes cyst formation occurs. It must be emphasized that such changes are generalized and if an x ray is taken of a given bone it will show involvement of the entire bone rather than a localized lesion surrounded by normal bone, such as in fibrous dysplasia. Frequently the first sign is a cystic lesion of the maxilla or mandible. Biopsy of this lesion or other cystic lesions may lead to an erroneous diagnosis of primary giant cell tumor In any such instance, parathyroid adenoma must be excluded. Unfortunately we have not been able to distinguish microscopically between lesions of the mandible secondary to hyperparathyroidism and those lesions that are independent and solitary In patients with hyperparathyroidism and bone changes the calcium and phosphorus levels in the blood may demonstrate prominent alterations from the normal. These chemical alterations are not nearly so important in the diagnosis as the

presence of an elevated alkaline phosphatase We have yet to see a patient v a functioning parathyroid tumor with radiographic evidence of bone changes ' did not have an elevated alkaline phosphatase. In the past, bone changes o became extensive, with deformity, formation of many cysts, and even fract (Fig 266)



Fig 266—Photomicrograph of osteitis fibrosa cystica. Note bone production an struction with cyst formation. The dark areas represent hemorrhage and giant cell f tion (Brown tumor) (Low power) (W U neg 49-4562)

Microscopically bone biopsy of such a lesion demonstrates bone destru bone formation, cyst formation, and so-called brown tumors. These brown tu show areas of hemorrhage and giant cells. This combination of microscopic ings should make the pathologist suspect a functioning parathyroid ade (Fig 267) With removal of the parathyroid adenoma there is a rapid re to normal (Figs. 268 and 269) We have seen such a reversal take place v a two-month period even with advanced alterations. If cyst formation has present repair of these lesions cannot take place, and small cysts may p (Fig 270)

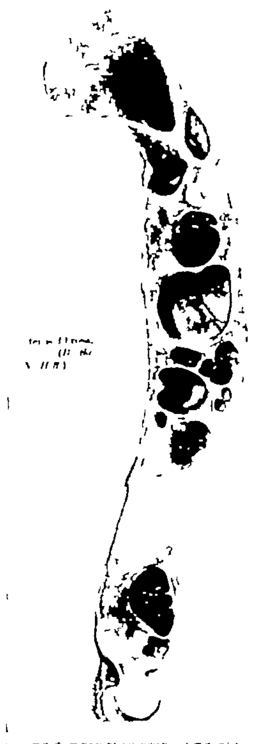


Fig. 267 —Gross photograph of extreme osteitis fibrosa cystica. Note deformity of the bone with numerous cysts and brown tumors. (W U neg 49-4586) (From Hunter D., and Turnbull, H. N Brit J Surg 19 203 1931)

SECONDARY HYPERPLASIA

Secondary hyperplasia of the parathyroid occurs with chronic renal disease such as renal rickets chronic pyelonephritis, multiple myeloma, diffuse metastatic carcinoma, and osteomalacia. Enlargement usually develops because of renal insufficiency with elevation of the phosphorus, secondary acidosis and resultant negative calcium balance with calcium flowing from the bone, causing secondary changes in the parathyroids. All of the glands usually become enlarged measuring



Fig 268—Roentgenogram demonstrating extensive changes in the bones of the pelvis and the femur caused by functioning parathyroid adenoma. (W U neg 49 3694) (From Black, B K. and Ackerman, L V: Cancer 3: 415-444 1950.)

Fig 269—Roentgenogram taken eight years following removal of the adenoma Note complete reversion to normal. (W U neg. 49-3695) (From Black B K., and Ackerman L. V Cancer 3 415-444 1950)

as much as 2 by 1 by 1 cm. but usually they do not reach the size of an adenoma they are creamy-gray rather than orange brown because the fat is replaced by cells. Because of this replacement of fat by cells there is not necessarily any enlargement of the glands

The microscopic appearance shows a prominent decrease of fat, but usually the intercellular fat tissue is not completely absent (Fig 271) Chief cells predominate and are of normal size Frequently there is an increased number of oxyphil cells which may grow to form areas of hyperplasia in rare instances this



Fig 270 —Photomicrograph demonstrating failure of repair of cystic lesions of the bone in hyperparathyroidism. This section was made twenty three months after removal of a functioning parathyroid adenoma. The patient died of renal insufficiency. This was one of the first cases successfully diagnosed and surgically treated in the United States. (Low power) (W U neg 49 5193)



Fig 271 —Photomicrograph of extreme secondary hyperplasia of the parathyroid. Note persistence of fat. There were large islands of oxyphil cells present. (×200.) (W U neg 49-5192)

hyperplasia can further progress to form a true adenoma (Gilmour) Castleman believes there is a higher glycogen content in the cells than is present in the adenomas or in hypertrophy of parathyroid tissue.

The bone changes in secondary hyperparathyroidism are similar to those in primary hyperparathyroidism, but are usually much milder in degree. Rarely severe bone changes occur with cyst formation (Morgan) The bony trabeculae are usually calcified and thus calcification is helpful in the differential diagnosis for it does not occur in Fanconi's syndrome or rickets.

PRIMARY HYPERTROPHY AND HYPERPLASIA

Primary hyperplasia and hypertrophy may also cause hyperparathyroidism characterized by extreme enlargement of all parathyroid tissue so that the total weight of the glands may exceed 65 grams We have seen a case in which the tissue removed weighed 125 grams (Fig 272) The enlargement is due to a combination of hyperplasia and hypertrophy of wasserhelle cells. Rogers has shown that even though the hypertrophy may exceed 60 times normal volume this alone could not be responsible for the size of the gland and therefore hyperplasia must be a contributing factor A distinct correlation may be made between the weight of the parathyroid tissue and the degree of hyperparathyroidism, a correlation which cannot be made with adenomas (Albright) The current evidence indicates that hyperparathyroidism depends upon a chronic hormone disorder but no evidence has been obtained to show that it is secondary to overactivity of the pituitary (Cope) It is possible that the stimulus is mediated through the autonomic nervous system. Whatever the mechanism involved the glands apparently respond to the stimulus by an all-or none reaction The treatment consists of the removal of all except about 200 mg of the parathyroid tissue. If this amount of tissue is left behind, recurrence of hyperparathyroidism is not likely and hypoparathyroidism will not develop Grossly one of the glands may be much larger than the others, but this is due to the relative original size of the glands, moreover glands may coalesce so that two glands appear as one. Another gross characteristic is the formation of pseudopods which may extend a considerable distance from the main mass of the gland. The upper pair are usually the largest (Castleman) These tumors are poorly encapsulated, grayish white, and quite soft. Cysts and hemorrhages have been observed.

Microscopically the most constant feature is the presence of very large clear cells the diameters of which may range from 10 to 40 microns (Fig 273) These cells may vary markedly in size however so that in some regions they do not appear much larger than the clear wasserhelle cells found in small numbers in normal parathyroid tissue. In most regions the cytoplasm of the cell is water clear, but in some cells small eosinophilic granules are present The nucleus averages from 6 to 7 microns there may be some variation in size but no giant nuclei are seen Basal orientation of the nuclei is one of the most common features. There may be considerable variation in the arrangement of these cells, the most frequent pattern being an alveolar distribution There may be areas of pseudoglandular formation, however and in other places a compact arrangement of the cells Large and

small cysts and areas of hemorrhage may be found. The connective tissue is sparse, appearing as delicate strands for the most part but in some areas it may be dense. *Chief cells* are rarely found. Chief cell hyperplasia is a new entity described by Cope and associates in which there is evidence of increased production of parathormone. They reported 10 cases. This abnormality is frequently seen in patients with multiple endocrine changes. In this entity all parathyroid glands are enlarged and tend to be reddish brown in color. The predominant cell is the chief cell but others are present. Usually no rim of normal parathyroid is present. Therefore treatment of these cases means subtotal removal of the glands.

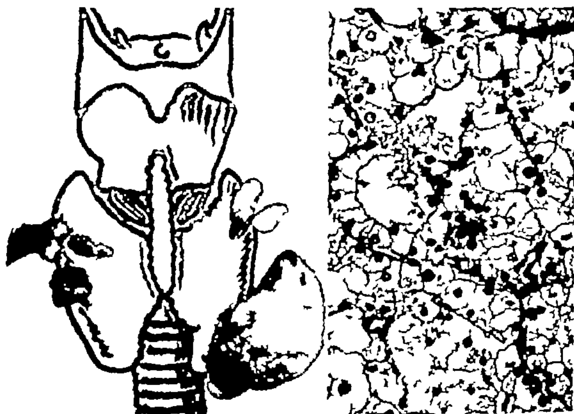


Fig. 272.—Distribution of parathyroid tissue in primary hypertrophy and hyperplasia in a 48-year-old woman. Total weight of the tissue removed was 125 grams. The patient died thirty five months after the first operation, and an equal amount of parathyroid tissue was again found. There were generalized diminished bone density and only mild hyperparathyroidism. (Courtesy Dr John Saxton, St. Louis Mo.)

Fig 273.—Photomicrograph of hypertrophy and hyperplasia. Note increase in size and number of wasserhelle cells. (High power.) (W U neg 49-5060.)

EXPLORATORY SURGERY

Walton and Cope have strongly emphasized the information a surgeon must have when he prepares to operate on a patient suspected of having a parathyroid adenoma. In the first place he must have a thorough knowledge of parathyroid physiology and in the second a complete knowledge of the appearance and possible location of the parathyroids in the neck and mediastinum. Cope pointed out that the parathyroids usually have a symmetrical distribution when one superior parathyroid is located in one place the opposite parathyroid will be in a

similar area. The statistical location of 197 tumors as reported by Norris in 1947 may aid the surgeon in his approach to an adenoma which cannot be palpated. Norris found that of those located in the neck 43 per cent were in the area of the right inferior gland, 41 per cent in the area of the left inferior gland 9 per cent near the right superior gland and 7 per cent near the left superior gland In his series 10 per cent were found in abnormal positions approximately two-thirds in the mediastinum, 30 per cent within the thyroid and the remainder in the area behind the esophagus. In our series 5 of 23 were located in abnormal areas, with 3 in the anterior mediastinum and 2 behind the esophagus

Operation must be as bloodless as possible in order that the anatomy not be disturbed and the parathyroids be identified If the patient does not have renal symptoms then the chances are high that there will be a single parathyroid adenoma and that because of the increased function of this gland the other glands will be atrophic. If an atrophic parathyroid is discovered this atrophy is presumptive evidence of the presence of a parathyroid adenoma (Cope) Cope has further stressed the imprudent removal of possible normal parathyroid tissue When normal parathyroids are removed at the time an adenoma is being investigated, the load thrown on the remaining parathyroid tissue may be too great and the patient may die in tetany The parathyroids are somewhat brown after puberty with increase in fat they become yellow If this fatty tissue is replaced with cells, the parathyroid tissue will become brown in color The vascular supply of the lower parathyroids comes from branches of the inferior thyroid arteries This supply is usually independent, a circumstance which may be helpful in locating abnormally placed parathyroid adenomas If one of these arteries is ligated infarction of the parathyroid may result (Walton) Because parathyroid glands are often discovered in unusual locations, such as within the thyroid (Black) anterior mediastinum, or behind the esophagus lymph nodes bits of adenomatous thyroid adenomas of the thyroid small nodules of fat and the thymus may be grossly erroneously identified as parathyroid adenoma. The diagnosis should easily be made with frozen section An adenoma usually is well delineated it may or may not have a capsule, and often there is a crescent of normal parathyroid gland. Frequently it is cystic, and there should be no difficulty in differentiating and diagnosing the relatively rare condition known as primary hypertrophy and hyperplasia. In these cases all parathyroid glands are prominently enlarged, and frozen section demonstrates the typical pattern of uniformly enlarged water-clear cells If it is known that the patient has normal renal function this clinical fact will make the diagnosis a certainty

CLINICOPATHOLOGIC CORRELATION

Nonfunctioning tumors of the parathyroid gland are rare and we are concerned principally with lesions that produce an excess of parathormone Cysts of the parathyroid arising usually from the inferior group cause no symptoms other than those related to pressure (Fisher) In patients with a functioning neoplasm the first sign or symptom is usually related to bone or renal changes. The clinical types of hyperparathyroidism are summarized by the group from the Massachusetts

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Fig 272 —Distribution of parathyroid tissue in primary hypertrophy and hyperplasia in a 48-year-old woman. Total weight of the tissue removed was 125 grams. The patient *died thirty-five months after the first operation, and an equal amount of parathyroid tissue* was again found. There were generalized diminished bone density and only mild hyperparathyroidism. (Courtesy Dr John Saxton St. Louis Mo.)

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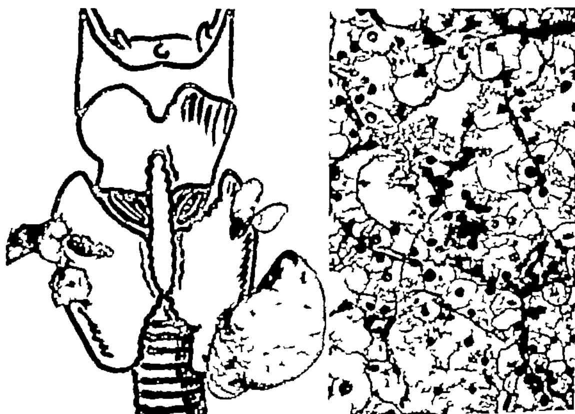


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General Hospital (Cope) (Table 8) The bone changes may first be apparent clinically in the mandible or maxilla and therefore first recognized by either an oral or plastic surgeon The true nature of the process may be recognized because of its diffuse nature with the characteristic radiographic alterations in the skull

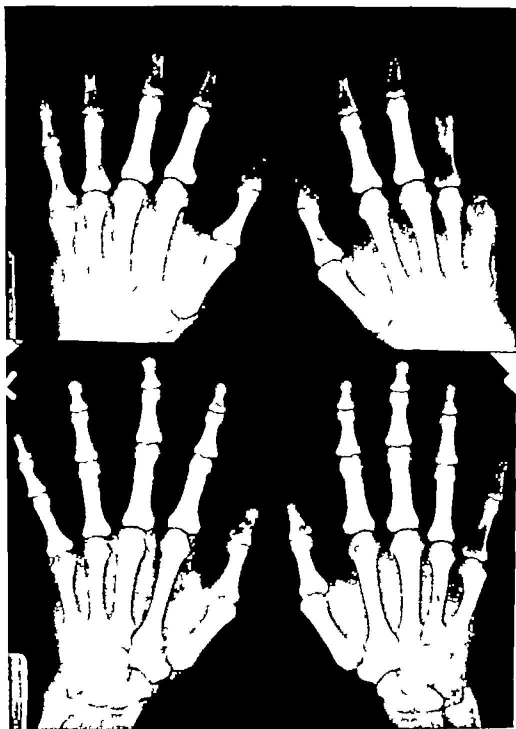


Fig 274—Radiographs of hands of a patient with a functioning parathyroid adenoma. The cystic changes and the cortical alterations seen in the upper radiographs have dramatically changed in the lower radiographs which were taken 9 months after the removal of the parathyroid adenoma. (W U negs. 57-6267 and 57-6268.)

and fingers (Fig 274) Invariably the parathyroid adenoma is not large enough to be felt clinically, but may be seen indirectly because of pressure deformities recognized radiographically in the esophagus or trachea Wyman localized 20 of 34 cases The larger the tumor, the more severe the disease, and Hellstrom reported some correlation between the size of the adenoma and the calcium level. Spontaneous remission of signs and symptoms can occur because of necrosis within an adenoma (Howard) Infrequently, functioning tumors of other endocrine glands such as the pituitary, pancreas adrenal and thyroid may be associated with a parathyroid adenoma (Underdahl) This association of multiple tumors of multiple endocrine organs may have a familial incidence (Moldawer) Duodenal ulcer occurred in 12 of 50 patients in Hellstrom's series The incidence of duodenal ulcer was highest in men It is interesting that Schiffrin demonstrated that parathyroid extract injected into dogs causes an increase in the volume acidity and pepsin content of gastric secretion With removal of the adenoma, the ulcer usually heals. Pancreatitis occurs with increased frequency in patients with functioning tumors of the parathyroid. Goldman has emphasized that in patients with functioning parathyroid adenomas who have minimal hypercalcemia and normal phosphate levels the tubular reabsorption of phosphate (TRP) was uniformly subnormal.

If a patient has a functioning tumor of the parathyroid he usually has a chronic disease which may not be recognized for several years The bone changes if extensive, may be associated with multiple fractures and force the recognition of the cause of this disability The most serious complication is the presence of renal changes If these changes are severe at the time of the removal of the parathyroid adenoma, they often continue to progress, are frequently associated with hypertension, and are the most important factor in prognosis.

TABLE 8 CLINICAL TYPES OF HYPERPARATHYROIDISM MASSACHUSETTS GENERAL HOSPITAL SERIES*

Bone Disease	
1 Classic	48
2 Decalcification	7
3 Decalcification and renal stones	30
No Bone Disease	
1 Renal stones	81
2. Peptic ulcer and renal stones	8
No Bone Renal or Ulcer Complication	1
	175

*From Cope O The Parathyroid Glands, in Allen, J G Harkins, H. N., Moyer C A. and Rhoads, J E Surgery Principles and Practice Philadelphia 1957 J B Lippincott Co

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INTRODUCTION

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Chapter 8

THYROID

INTRODUCTION

THYROGLOSSAL DUCT CYST BRANCHIAL CLEFT CYST AND HETEROTOPIC THYROID

SPECIFIC INFECTIONS OF THE THYROID

- Syphilis
- Tuberculosis

ACUTE AND SUBACUTE THYROIDITIS (STRUMA FIBROSA)

INVASIVE THYROIDITIS (RIEDEL'S STRUMA)

- Clinicopathologic Correlation

HASHIMOTO'S DISEASE (STRUMA LYMPHOMATOSA)

- Clinicopathologic Correlation

HYPERPLASIA OF THE THYROID (EXOPHTHALMIC GOITER, GRAVES DISEASE)

- Clinicopathologic Correlation

ADENOMATOUS THYROID WITH AND WITHOUT HYPERPLASIA (NODULAR GOITER WITH AND WITHOUT HYPERPLASIA)

- Clinicopathologic Correlation

COLLOID AND CONGENITAL GOITER

CLASSIFICATION OF THYROID NEOPLASMS

- Benign Tumors
  - Simple Adenoma
  - Hürthle Cell Adenoma
- Gross and Microscopic Evidence of Malignant Change in an Adenoma
- Frozen Section
- Malignant Tumors
  - Papillary Adenocarcinoma
  - Papillary Adenocarcinoma—So-called Lateral Aberrant Thyroid
  - Alveolar Type Adenocarcinoma
  - Small Cell Carcinoma
  - Giant Cell Carcinoma
  - Rare Tumors
    - Hürthle Cell Carcinoma
    - Occult Sclerosing Carcinoma
    - Squamous Carcinoma
    - Plasmacytoma
    - Lymphosarcoma
    - Fibrosarcomas and Teratomas
  - Metastatic Carcinoma

CLINICOPATHOLOGIC CORRELATION

INTRODUCTION

The pathology of the thyroid gland is confused chiefly because of the alterations in the gross and microscopic patterns These changes have been influenced by the presence or absence of adequate iodine intake so that the pathology of the thyroid in different areas of the world varies In the United States such differences have been erased at least in part because of iodized salt. Classification of thyroid disease has also been in a chaotic state particularly from the viewpoint of neoplasms.

The thyroid parenchyma is not arranged in lobules, for in reconstruction models as shown by Rienhoff, follicles or vesicles are closed cavities not communicating with each other These vesicles may vary in size from 20 to 100 microns and have an epithelial lumen which is filled with a stainable substance called colloid. The epithelial lining rests on fine connective tissue in which there are capillary blood vessels lymphatics and nerves. There is no true basement membrane and probably no interfollicular epithelium

THYROGLOSSAL DUCT CYST, BRANCHIAL CLEFT CYST, AND HETEROTOPIC THYROID

> The thyroid anlage appears in the 2.0 to 2.5 mm. embryo as a midline structure projecting downward from the pharynx between the first and second branchial arches. This point of origin corresponds to the foramen cecum in adult life The midline thyroid anlage then descends in the course of development to its position in the anterior neck In the normal course of events, any connection between the cervical thyroid and its point of origin at the base of the tongue is obliterated and disappears However in certain instances remnants of the strand of tissue connecting these points may remain along with portions of the epithelial lining of the mouth cavity which have been dragged downward as the thyroid descends to persist as definite structures and form cysts sinuses, and fistulae found in later life (Stahl)

The hyoid bone formed from the second arch appears in the embryo following the descent of the thyroid and links with the thyroglossal remnant. This bone divides the tract into an infra and suprahyoid portion. The tract passes anteriorly posteriorly or through the bone. The cyst and sinuses of thyroglossal origin are lined by pseudostratified and ciliated columnar cells a squamous lining and mucous glands may be present (Fig 275) An inflammatory process is common. The commonest abnormality is a midline cyst usually in the region of the hyoid bone. The sinuses may develop from the suprasternal notch to the region of the hyoid bone. In order to adequately treat this lesion it is essential that the tract be completely removed from the foramen cecum with resection of the central portion of the hyoid bone. A cyst may develop because there is secretion from the cells lining the tract. If the foramen cecum remains open, the tract may become directly infected Under pressure sinuses will develop (Rees) These cysts are most common in childhood but may assume clinical significance even after the age of fifty (Brintnall)

Branchial cleft cysts and sinuses may appear in the anterior lateral neck from the preauricular region to the clavicle. A cyst or sinus appearing in the preauricular area or beneath the posterior one half of the mandible usually is derived from the first branchial cleft and may have a connection into the external auditory canal These lesions are rare. Lesions appearing just anterior to the sternocleidomastoid muscle in the lower half of the neck probably are remnants of the second branchial cleft These may have an open squamous lined tract which communicates with the pharynx near the superior fold of the tonsil. These cleft defects may consist of patent pharyngocutaneous fistulas simple sinuses and blind cysts Cysts also

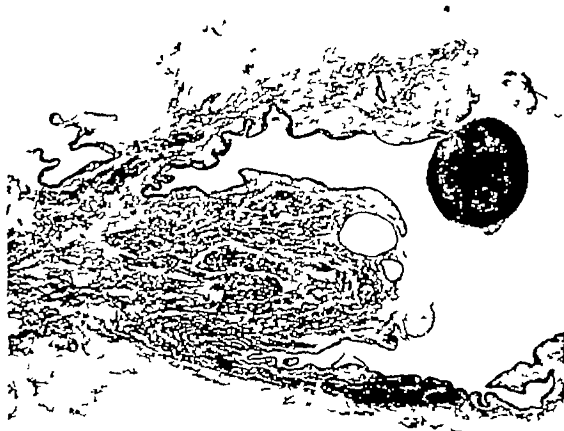


Fig 275.—Photomicrograph of a thyroglossal duct cyst. Note lymphoid tissue epithelial lining and cystic spaces. (Low power) (W U neg 50-2857)

occasionally occur with a communication into the pharynx, but none to the skin (Lyall) The lining of these cysts and fistulous tracts is usually squamous epithelium, but columnar and columnar ciliated epithelium are common. Abundant lymphoid tissue often with germinal centers is observed beneath this epithelium. Mucous glands are rare. Infection may complicate the microscopic picture. We do not believe that epidermoid cancer arises in branchial cleft cysts. Any cystic mass in the neck containing squamous cancer must be considered a lymph node metastasis with cystic degeneration.

If there is faulty descent of the thyroid, the gland may be situated anywhere along the course of the duct (Ray) The most frequent location of this heterotopic tissue is in the region of the base of the tongue or the pharyngeal portion of the

foramen cecum. Very rarely a lingual thyroid may be present anteriorly in the tongue (Rosedale) or within the larynx (Beeson) (Fig 276) Rather frequently there is prolongation of the thyroid into the substernal region, and thyroid tissue may also be found free in the anterior mediastinum rarely in the posterior mediastinum (Sweet) (see Mediastinum)

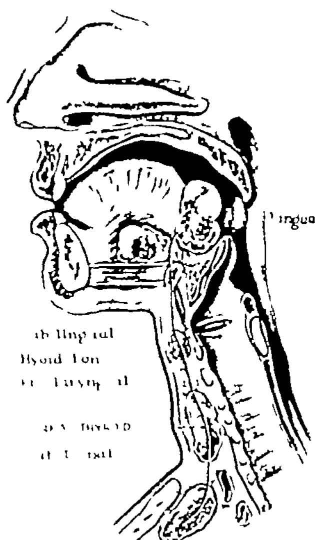


Fig 276—Distribution of heterotopic thyroid. (W U neg 50-1570) (From Lemmon W T and Paschal G., Jr Am. J Surg 52 82-85 1941)

Grossly the thyroid tissue found in such heterotopic nodules does not differ from that found elsewhere. When such tissue is located near the base of the tongue, there may be an imperfect capsule with nodules of thyroid between muscle bundles this may cause confusion and may result in an erroneous diagnosis of carcinoma (Wapshaw) Although aberrant thyroid tissue is usually benign carcinomas have been reported (Tyler Ashhurst)

Patients with lingual thyroids have some difficulty in swallowing and some degree of pharyngeal and laryngeal obstruction (Fig 277) We have seen an infant die of respiratory insufficiency because of a large unrecognized lingual thyroid. Lingual thyroids appear during puberty and adolescence about 150 cases have been reported (Montgomery) When heterotopic thyroid tissue is present,

complete absence of thyroid in its normal location occurs in approximately 70 per cent of instances. Therefore, with removal of heterotopic thyroid, myxedema appears in a high percentage of instances



Fig. 277—Clinical photograph of a young girl with heterotopic thyroid. (W U neg. 49 1754)

SPECIFIC INFECTIONS OF THE THYROID

Syphilis

Syphilis of the thyroid is rare. Grossly the lesion is asymmetrical and frequently hard and in its extension may cause fixation of the thyroid to the surrounding structures with even paralysis of the recurrent laryngeal nerve. This lesion is a manifestation of tertiary syphilis Children may also have gummatous *nodules of the thyroid associated with syphilitic visceral lesions. Microscopically* the lesion is a nodular gummatous process Clinically it is often thought to be carcinoma.

Tuberculosis

Tuberculosis as a primary clinical manifestation within the thyroid gland is a pathologic rarity In disseminated miliary tuberculosis it is not rare for an occasional tubercle to occur within the thyroid gland. It is also possible for tuberculous cervical lymph nodes or tuberculous involvement of the larynx to involve the thyroid gland secondarily In the past, tuberculosis was frequently diagnosed within the thyroid because of the presence of giant cells which were secondary to some nonspecific inflammatory process within the thyroid gland.

ACUTE AND SUBACUTE THYROIDITIS (STRUMA FIBROSA)

This relatively common form of thyroiditis is probably related to infection most commonly from the oral cavity. There also may be distant infections with metastatic foci in the thyroid. It is common for repeated attacks of sore throat, laryngitis or an infected tooth to precede the development of the lesion (Clute).

Grossly the process usually involves the entire gland but the clinical involvement is often asymmetrical. The thyroid is usually increased to approximately

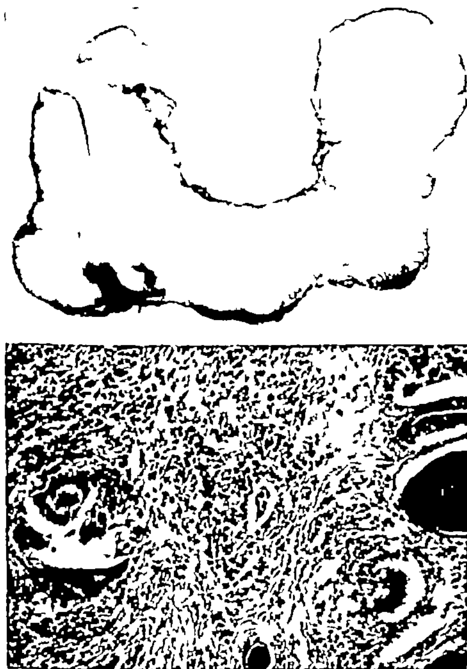


Fig. 278.—Gross photograph of cross section of a thyroid with diffuse chronic thyroiditis. Note preservation of normal symmetry and the presence of a capsule. There were minimal pressure signs and symptoms. (W U neg 49-868.)

Fig. 279.—Photomicrograph of chronic thyroiditis with fibrosis, chronic inflammation and foreign body giant cell reaction. (×180.) (W U neg 49 2022.)

two times the normal size. Focal grayish areas are observed in the thyroid but colloid can still be made out. In the advanced stage of the process the involved areas are firm (Fig 278) In contrast to Riedel's struma there is usually little or no adherence to the surrounding structures.

The microscopic changes have been well described by de Quervain. Frequently there are focal areas of acute inflammation even microabscesses and granulomatous zones are present Giant cells are common, and these are often seen engulfing colloid (Fig 279) The same thyroid may show variable stages of the same picture This is a condition which, because of the presence of the giant cells, has been mistaken for tuberculosis. For that reason in the past it was designated as pseudotuberculous involvement of the thyroid gland

Early in the evolution of this process the throat may be sore, there may be severe pain on swallowing and the thyroid may be extremely tender Cases of thyroiditis are often explored for carcinoma inasmuch as after the acute process has subsided pressure symptoms hypothyroidism and suggestive signs of malignancy may occur Thyroiditis can rarely occur with papillary carcinoma and be confusing clinically and pathologically (Crile) The diagnosis is usually made by frozen section at the time of surgical exploration The best form of treatment has not been standardized ACTH and cortisone have proved valuable in our experience. Irradiation therapy has not been too successful Frequently subtotal thyroidectomy is done.

TABLE 9 GROSS AND MICROSCOPIC CHARACTERISTICS OF SUBACUTE THYROIDITIS HASHIMOTO'S DISEASE, AND INVASIVE THYROIDITIS

	SUBACUTE THYROIDITIS	HASHIMOTO'S DISEASE	INVASIVE THYROIDITIS (RIEDEL'S STRUMA)
Gross characteristics			
Consistency	Firm	Firm	Extremely firm
Involvement	Diffuse	Diffuse	Asymmetrical
Adherence to surrounding structures	Delicate if present	Delicate if present	Strongly adherent
Microscopic characteristics			
Microabscesses	Present	Absent	Microabscesses absent
Lymphoid tissue	Minimal infiltration	Present throughout with germinal centers	Minimal
Giant cells	Common	Rare	Absent
Fibrous tissue	Increased	Slightly increased fine with even distribution	Extremely prominent

INVASIVE THYROIDITIS (RIEDEL'S STRUMA)

Riedel's struma was described by Riedel in 1896 Joll reported finding an incidence of about five times as many cases of Hashimoto's disease as Riedel's struma. While the disease predominates slightly in females, it has approximately the same predominance as other diseases of the thyroid in similar geographic areas. It usually occurs at an earlier age than Hashimoto's disease and much less frequently (Joll) Its pathogenesis is obscure but most authorities believe it is an independent entity bearing no relation to Hashimoto's disease. It also appears to bear no relation to subacute thyroiditis.

Grossly the process is asymmetrical and involves only localized areas of the thyroid. It is stony hard in consistency and the thyroid is fixed to surrounding structures. At the time of operation there is greatly increased resistance around the capsule of the thyroid and dense fibrous strands extending from this capsule are intermingled with muscle which may have to be severed. On cross section it cuts with greatly increased resistance and the fibrosis which is present may completely obliterate the normal architecture. Outside a poorly demarcated zone the thyroid usually appears quite normal and colloid may be seen.

Microscopically there is complete fibrous replacement of the involved area which is frequently extensively hyalinized. Muscle cells in the immediate area are often directly infiltrated by this connective tissue. Giant cells are absent and there is no evidence of acute inflammation.

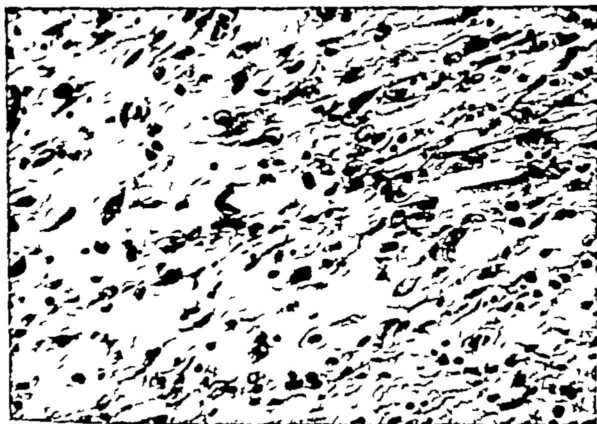


Fig. 280.—Photomicrograph of invasive thyroiditis with extensive fibrosis and chronic inflammatory cells. No residual thyroid can be identified. (×370.) (W U neg 57-4809.) (Slide contributed by Dr L. Woolner Mayo Clinic Rochester Minn.)

Clinicopathologic Correlation

Riedel's struma is not preceded clinically by an acute inflammatry process or by tenderness of the thyroid gland. It is almost impossible to differentiate it clinically from carcinoma of the thyroid. It binds the surrounding structures of the neck in an iron collar and may compress the trachea to a slitlike state. Patients frequently have profound dyspnea, particularly in a recumbent position. Frozen section is diagnostic in differentiating this condition from carcinoma. If a definitive diagnosis can be made it is wise to resect the area surgically for this lesion is

focal and resection results in relieving the obstructive symptoms. At the time of resection the surgeon may find no point of cleavage and may tear into a large vein and have to sever adjoining muscles in order to remove the involved thyroid. The regional lymph nodes do not become involved, a factor which may provide a clue to the diagnosis. Hypothyroidism does not usually follow resection. Riedel's struma is a rare lesion and Woolner was able to find only 20 cases in the Mayo Clinic files between 1920 and 1955 There was only one case per 2,000 thyroidectomies (Fig 280)

HASHIMOTO'S DISEASE (STRUMA LYMPHOMATOSA)

Struma lymphomatosa was first described by Hashimoto in 1912 and the clinical and pathologic description of his four cases is still classical. There has been little further information added since that time. The pathogenesis of this condition is obscure, although Hellwig believes that it is a functional disorder in which the cycle of colloid storage and release is fundamentally disturbed. Exhaustion of colloid explains the symptoms of hypothyroidism, and the underlying cause is probably an excess of thyrotrophic hormone Williamson believes that physiologically the thyroid is a subnormal gland undergoing compensatory lymphoid hyperplasia with a lymphocyte reaction proportional to the failure of the usual function of epithelial hyperplasia. The final microscopic pattern is the result of exhaustion atrophy This condition is predominantly a disease of females over the age of 40 and bears no relation to Riedel's struma which occurs usually at a later age. In Marshall's 114 cases of Hashimoto's disease 112 were females. Biopsies taken at different time periods usually reveal a similar histologic picture (McClintock) Graham, Joll and McSwain support the concept that Hashimoto's disease is a separate entity from Riedel's struma.

Grossly the entire gland is involved by disease and enlarged proportionately It is asymmetrical only when the lobes of the thyroid are asymmetrical. It has a *firm but not stony hard consistency* The *fascial attachment* between the thyroid gland and the tracheal wall is at times slightly thickened, but there is no strong fixation On section early lesions are quite friable and the gland has a pseudolobulation with a pale pink and yellowish white color The cross section looks somewhat like a hyperplastic lymph node replaced by grayish yellow material (Fig 281) Necrosis abscess, and calcification are absent, and colloid is not clearly discernible.

Microscopically there is diffuse infiltration by lymphoid tissue, and invariably there are large follicles with definite germinal centers (Fig 282) This lymphoid tissue is both inter and intralobular in its distribution The surrounding acini are small and invariably atrophic, and quite frequently the cells which form these acini are large with acidophilic cytoplasm. Foreign body giant cells are not frequent Connective tissue when present is evenly distributed and is seen only in the advanced stages of the disease The lymphoid infiltration in Hashimoto's disease must be distinguished from that seen in hyperplastic thyroids. Usually however the lymphoid tissue in hyperplasia does not have germinal centers and furthermore, while lymphoid infiltration may be present, there are always areas

which show the characteristic microscopic pattern of hyperplasia. In 40 per cent of patients with simple colloid goiters between the ages of 20 and 40 there may be areas of lymphoid hyperplasia but none have germinal centers (Simmonds)

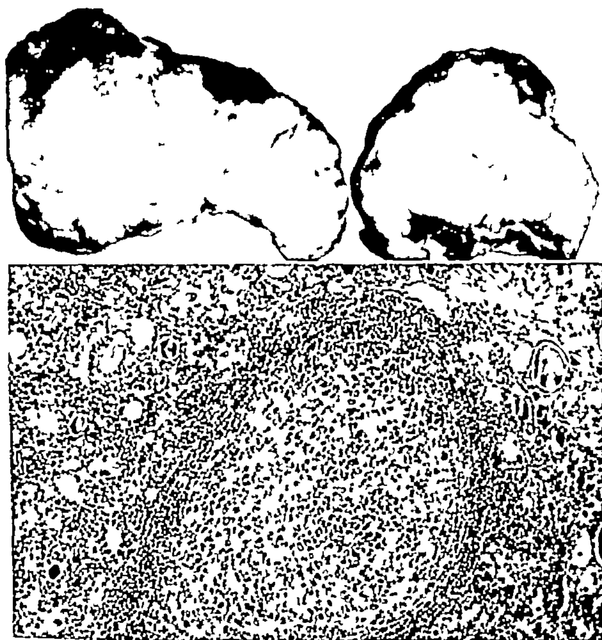


Fig. 281—Gross photograph of Hashimoto's disease in a child. Cut section demonstrates homogeneous yellowish gray areas and these represent increased lymphoid tissue. (W U neg 50-1462)

Fig. 282—*Photomicrograph of Hashimoto's disease (lymphadenoid goiter) Note increased lymphoid tissue with germinal center* (×150) (W U neg 50-683)

Doniach has demonstrated that the serum of patients with Hashimoto's disease contains auto-antibodies against thyroglobulin The antibody is organ specific. She states

Thyroglobulin precipitins were also found in the sera of 6 patients with spontaneous nongoitrous myxedema and 4 patients with subacute

(giant-cell) thyroiditis No precipitins were found in the sera of 238 patients with various thyroid disorders. It is suggested that destruction of the thyroid in Hashimoto's disease results from progressive interaction of the auto-antibody with thyroglobulin in the gland and that lesser degrees of lymphoid infiltration found in other thyroid diseases may represent a localized immune response.

Clinicopathologic Correlation

Hashimoto's disease causes clinical diffuse, firm enlargement of the thyroid, usually with a few signs of pressure, such as slight compression of the trachea or slight dyspnea when the patient is lying down At operation the thyroid is usually quite easily separated from other structures. Because of the firm character of the lesion, it may be confused with carcinoma, but the diffuse involvement without fixation to the surrounding structures should be strong evidence against it. The diagnosis is usually made on frozen section and subtotal thyroidectomy done. The resulting hypothyroidism can be controlled with thyroid extract

The diagnosis of Hashimoto's disease is relatively simple when it conforms to the above gross and microscopic patterns There are numerous examples how ever *in which there are focal areas of lymphoid tissue with perhaps slight evidence* of hyperplasia. In such instances we have dismissed the lymphoid hyperplasia as a simple accompaniment of the hyperplasia. We do not know the pathogenesis of Hashimoto's disease neither do we have evidence that it ever becomes Reidel's struma or that patients with Hashimoto's disease ever have pre-existing thyrotoxicosis. In 20 instances of Hashimoto's disease reported by Heptinstall, none had thyrotoxicosis and none had passed through a toxic phase. In a study made at our institution by Spjut the minimal histologic findings for a diagnosis of Hashimoto's disease (struma lymphomatosa) include a diffuse, or almost diffuse, oxyphilic transformation of the follicle epithelium, the presence of lymphoid follicles and fibrosis of the stroma. In a study of thyroid specimens removed at interval operations in 76 cases of Graves disease, and toxic (non exophthalmic) and nontoxic goiters we were unable to demonstrate convincingly progression of thyroid hyperplasia to struma lymphomatosa chronic thyroiditis, or Reidel's struma. Papillary carcinoma may be associated with Hashimoto's disease (Dailey)

HYPERPLASIA OF THE THYROID (EXOPHTHALMIC GOITER, GRAVES DISEASE)

The pathogenesis of exophthalmic goiter (Graves disease) is not well understood. The undulatory changes due to thyrotrophic hormones acting on the thyroid with its release of thyroxin must influence pathologic changes. With release of thyroxin an inhibition of thyrotrophic hormone occurs. In order for thyrotoxicosis to appear there must be some fundamental upset in this reciprocal arrangement. At that time the secretion of thyroxin may get out of control and the syndrome of florid Graves disease appears. The onset may be related to psychogenic factors. For instance, during the 1929 stock market panic there was a great increase in the incidence of Graves disease. The history of any one of these pa

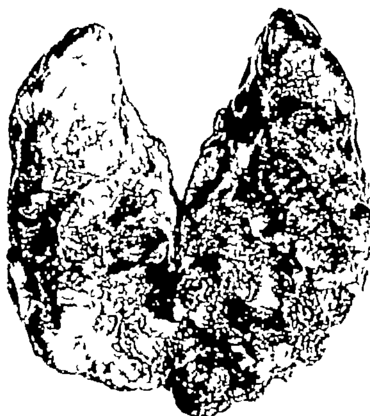
tients usually discloses some severe emotional stress immediately preceding the onset of disease

Grossly the smooth symmetrical gland of hyperthyroidism is not much enlarged as a rule The changes in the gland may be altered by preoperative therapy Lugol s solution and/or propylthiouracil or related compounds tend to produce involutionary changes propylthiouracil and its related compounds block the release of thyroxin and cause rapid disappearance of symptoms. The gland itself however is still grossly and microscopically unchanged and bleeding from it may be difficult to control For this reason propylthiouracil therapy and Lugol s solution are given together for approximately ten days before the operation. The gland is usually succulent and vascular and on section has the consistency of pancreatic tissue It is of uniform color with shades of brown yellow gray or red varying with vascularity colloid content and hyperplasia (Fig 283) Usually the follicles can be made out If the disease is of long duration the gland is often friable uniform and dull yellow in color

Microscopically the changes which allow a diagnosis of hyperplasia rest primarily on epithelial alterations The prominence of these epithelial changes depends on the degree of hyperplasia and the response of the gland to therapeutic measures tending to produce involution (Lugol s solution x ray therapy) In the resting gland the individual cells are flat cuboidal with nuclei resting at the base. With increased activity the nucleus becomes larger and gravitates toward the center of the cell There is also proliferation of epithelium which becomes columnar in character often with infolding of the epithelium. Papillary proliferation may be seen as the gland becomes increasingly vascular (Fig 284) This epithelial proliferation may at times be so pronounced that an inexperienced pathologist may be tempted to call the changes carcinoma In fact it may be so extreme that papillary epithelial proliferation will extend into contiguous muscle (Meissner) Even with pronounced involutionary changes if enough sections are cut, the pathologist can usually determine the presence of pre-existing hyperplasia Other changes supporting the diagnosis of hyperplasia include the following the colloid in a hyperplastic gland is somewhat pale and usually shows peripheral vacuolation and there are often aggregations of lymphoid tissue present without germinal centers. The changes in the colloid and the presence of the lymphoid tissue support the diagnosis of hyperplasia This lymphoid tissue persists after involution. If the process is of long duration the connective tissue is increased. In primary hyperplasia cells may be present with foamy cytoplasm. These cells may also be present in adenomatous goiters and rarely in tumors. In some instances the fat and glycogen stains are positive (Meissner)

Clinicopathologic Correlation

Classical Graves disease usually appears in a highly emotional nervous patient and is accompanied by the typical eye signs The basal metabolic rate is markedly increased and with this there is often a great increase of appetite. The heart rate may be rapid there is a wide variation in pulse pressure and often auricular fibrillation is present In advanced disease cardiac failure may occur and there



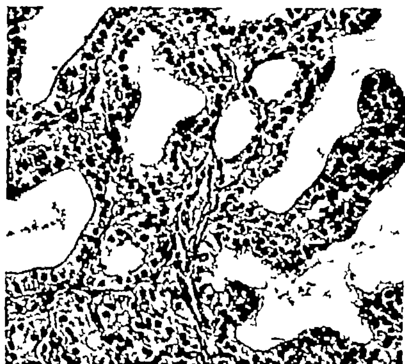


Fig 283 —Gross photograph of thyroid in exophthalmic goiter (hyperplasia) The thyroid is diffusely enlarged hyperemic, and without nodules. (W U neg 48-5014)

Fig. 284 —Photomicrograph of hyperplasia of the thyroid Note solid masses of cells, high columnar epithelium, and papillary infolding (High power) (W U neg 48-3404)

may be liver damage Muscular weakness weight loss and increased resting pulse rate are important clinical manifestations. Elevation of the serum protein bound iodine and the increased radioactive iodine uptake are the most objective laboratory examinations supporting diagnosis of Graves disease All these clinical signs and symptoms with the exception of exophthalmos, dramatically subside under appropriate therapy By use of radioactive iodine Goode demonstrated that even after the most radical operation one fifth the normal uptake could be expected within one year Unfortunately this is not true for other types of thyroid pathology and in Hashimoto's disease progressive atrophy takes place Furthermore if a hyperplastic gland is removed and microscopically it shows evidence of thyroid exhaustion (oxyphilia and lymphocytic infiltration), this patient has a greater chance of developing myxedema

ADENOMATOUS THYROID WITH AND WITHOUT HYPERPLASIA (NODULAR GOITER WITH AND WITHOUT HYPERPLASIA)

The incidence of adenomatous thyroids or nodular goiter will depend to a great extent on the geographic distribution of patients Of 544,918 patients in the Boston City Hospital the Massachusetts General Hospital and Johns Hopkins Hospital only 0.59 per cent were admitted for goiter (Rogers) By contrast of 68,573 admissions to the Illinois Research Hospital (during 11.5 years) there was an incidence of 1 7 per cent nodular goiters (roughly 3.5 times that on the Atlantic Seaboard) (Cole) In areas of endemic thyroid disease some degree of nodular thyroid will inevitably be found at postmortem examination There will naturally be considerable discrepancy between clinical nontoxic nodular goiter and the almost 100 per cent frequency of such disease at postmortem examination in endemic areas.

Grossly the appearance of a nodular nontoxic thyroid is distorted by the areas of nodulation one lobe frequently being much larger than the others The capsule of the lobe is usually intact. On cross section there are multiple areas of hemorrhage and calcification. The individual nodules within the lobe are frequently surrounded by an incomplete fibrous tissue encapsulation, and the variable sizes of the colloid follicles can readily be seen It is not too rare for a large cystic area of degeneration in which hemorrhage has occurred to be removed as a dominant nodule. Because of the increased frequency of carcinoma in these thyroids it is important that the gross specimen be fixed first and step sections made in order to discover any questionable areas of malignancy These thyroids are removed most commonly because of pressure signs or cosmetic symptoms increased evidence of thyrotoxicosis in females at the menopause and finally because of the increased chance of carcinoma. Such nodular glands may be located substernally (Figs. 285 and 286)

Microscopically adenomatous thyroids present a variable picture. The follicles vary tremendously in size giant follicles are frequently seen. These follicles are lined by flattened epithelium. With progress of the changes, colloid is released into the interstitial tissue where it provokes a variable reaction Frequently there are areas of recent as well as old hemorrhage often with deposits of hemo-

Fig 285 —Roentgenograms of a large anterior mediastinal adenomatous thyroid (W U neg 49 5739)

Fig 286.—Gross photograph of the large substernal adenomatous thyroid shown in Fig 285 Note nodulation hemorrhage, and cyst formation (W U neg 49-6863)



Fig 287 —Gross photograph of an adenomatous thyroid with moderate hyperplasia. There are nodulation and cellular areas. (W U neg 48-5204)

siderin pigmentation Coarse trabeculae of fibrous tissue completely separate the lobules Areas of calcification are commonly present but bone formation is rarely found There may be greatly thickened vessels around the periphery of the gland often showing calcification of their media

The nodular gland may show some microscopic evidence of hyperplasia, but it is frequently difficult to determine clinically whether or not there is any increase in thyroid activity (Fig 287) The microscopic findings of hyperplasia of the thyroid are the same as those seen in the primary hyperplasia although the changes are not generally as marked If multiple sections are taken and there are areas of hyperplasia, the usual microscopic alterations will be seen. It is probable that small localized areas of hyperplastic epithelium in a nodular thyroid should not be accepted as reliable evidence of thyrotoxicosis. The prominent eye signs of Graves disease do not occur in the nodular toxic goiter

Clinicopathologic Correlation

The nodular thyroid, particularly the one without evidence of hyperplasia may manifest itself as a single, firm, dominant lump which clinically may exactly simulate a neoplasm However if the tumor is soft and poorly defined and waxes and wanes with physiologic function, the chances are great that it is not malignant. The fully blown nodular thyroid may become very large, cause some degree of tracheal obstruction and produce considerable facial disfigurement, for these reasons it should be removed When hyperplasia is present, there is very little chance that carcinoma is coexistent, for the association of carcinoma and hyperplasia in the thyroid is probably not related (Pemberton) It is only with clinically demonstrable, nodular nontoxic thyroids that the frequency of carcinoma reaches an important figure. Table 10 compiled by Cole demonstrates the association between

TABLE 10 INCIDENCE OF CARCINOMA IN NODULAR GOITER AS OBTAINED FROM NUMEROUS REPORTS IN THE LITERATURE*

AUTHOR	NUMBER OF PATIENTS WITH NODULAR GOITER (TOXIC AND NONTOXIC)	PER CENT OF CARCINOMA IN NODULAR GOITER (TOXIC AND NONTOXIC)	NUMBER OF PATIENTS WITH NODULAR NONTOXIC GOITER	PER CENT OF CARCINOMA IN NODULAR NONTOXIC GOITER	PER CENT OF CARCINOMA IN SOLITARY NONTOXIC NODULAR GOITER
Horn and associates Philadelphia, Pa. 1947	1 135	6 3	637	9 8	
Ward San Francisco Calif 1947	3,539	4.8			15 6
Crile Cleveland Ohio 1948	537	5 6	?74	10 9	24.5
Cole and associates Chicago Ill. 1948	663	8 0	?85	17 1	24 4

*From Cole, W H Slaughter D P., and Majarakis J D : Surg. Gynec. & Obst. 89-349 356 1949

various types of thyroid disease and cancer It should be noticed that both Crile and Cole show a high percentage of carcinoma in association with solitary non toxic nodular goiter Their reliable statistics indicate the necessity of exploration and removal of such single solitary nontoxic nodules.

COLLOID AND CONGENITAL GOITER

Diffuse colloid goiter is an expression of iodine lack, and it is infrequent in the United States even in endemic areas because of the use of iodized salt The thyroid glands are diffusely enlarged and simply show enlarged follicles filled with colloid. For the same reason given above congenital goiter in the United States is extremely rare. In Switzerland before the obligatory use of iodized salt it was common Its occurrence is related to iodine lack and a child showing such change

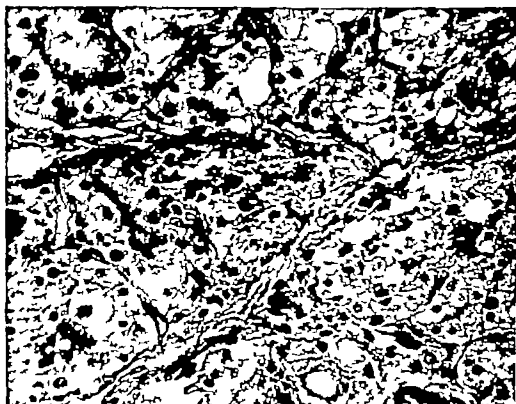


Fig 288 —Photomicrograph of congenital goiter (weight 40 grams) Note uniform cells and scanty colloid. (×360) (W U neg 53-395)

may have a "goiterous mother (Hiilesmaa) Because such goiters regress with iodine therapy it is rare that a surgical pathologist has the opportunity of seeing one. A thyroid weighing over 5 grams in a newborn child would be abnormal. We have seen a large congenital thyroid in which the specimen weighed 40 grams and was symmetrically enlarged. Microscopically it showed small follicles, many of which were empty of colloid (Fig 288) In the cretin hormone synthesis does not occur There is failure of iodine utilization and only minimal colloid or iodine poor colloid is formed.

CLASSIFICATION OF THYROID NEOPLASMS

A Benign tumors
  1 Adenoma
    a. Simple
    b. Hürthle cell type
B Malignant tumors
  1 Adenocarcinoma
    a. Papillary type (so-called lateral aberrant thyroid)
    b. Alveolar type (follicular type)
  2. Carcinoma
    a Small cell type
    b Giant cell type
  3 Rare tumors
    a. Hürthle cell carcinoma
    b. Epidermoid carcinoma
    c. Plasmacytoma
    d. Lymphosarcoma
    e Fibrosarcoma
    f Teratoma
  4 *Metastatic carcinoma*

The frequency of various types of carcinoma of the thyroid is shown i two large series studied by Frazell at the Memorial Hospital (Table 11) ar Meissner from the Lahey Clinic (Table 12)

TABLE 11 A STUDY OF THREE HUNDRED AND ONE CANCERS OF THE THYROID

	NO OF CASES	PER CENT
1 Papillary adenocarcinoma	139	46
2. Follicular and alveolar adenocarcinoma	22	7
3 Solid adenocarcinoma	56	19
4 Giant-cell carcinoma	39	13
5 Hürthle-cell carcinoma	27	9
6 Unclassified†	18	6
Total	301	100
(Lymphosarcomas and squamous carcinomas omitted)		

*From Frazell, E. L., and Foote F W J Clin Endocrinol. 9 1025-1030 194
†*Histologic material not adequate to classify*

Benign Tumors

Simple Adenoma.—There have been numerous classifications of ader with many subdivisions but any breakdown into individual types is probabl justified. For instance, the so-called colloid adenoma is usually not a true plasm but simply represents a poorly defined and partially encapsulated foc nodular goiter The *terms fetal and embryonal* adenomas are erroneous cl cations in that these tumors are not present at birth but develop at a later period they are probably variations of the same neoplasm. It would be i better to classify them *simply as adenomas*

Nodules of adenomatous thyroid are still being diagnosed as adenomas or neoplasms so that when the question What percentage of adenomas be malignant?" is asked the figure is much lower than the true incidence. It

TABLE 12 A STUDY OF FOUR HUNDRED AND THIRTY NINE CANCERS OF THE THYROID*

	NUMBER OF CASES		PER CENT
Group 1—Adenoma with invasion	108		24 6
a. Blood vessel invasion		12	
b. Capsular or lymphatic invasion		61	
c. Capsular or lymphatic plus blood vessel invasion		35	
Group 2—Adenocarcinoma	203		46.2
a. Papillary type		154	
b. Alveolar type		49	
Group 3—Carcinoma simplex	108		24 6
a. Small-cell type		72	
b Giant-cell type		36	
Miscellaneous	20		4 6
a. Hürthle-cell		7	
b Fibrosarcoma		7	
c. Lymphoma		3	
d. Epidermoid		2	
e Unclassified		1	
Total		439	100

*From Meissner W A and Lahey F H J Clin. Endocrinol. 8 749-761 1948



Fig 289—Gross photograph of a sharply circumscribed cellular adenoma of the thyroid with central hemorrhage. Note sharp demarcation between this adenoma and the normal thyroid. (W U neg. 52 2706.)

seems quite certain that if strict pathologic criteria are used in the diagnosis of adenomas approximately 10 per cent of these lesions will be malignant (Meissner)

The criteria for the diagnosis of adenoma should be very rigid and accurate and should include the following the adenoma should have *complete* fibrous encapsulation it should be dissimilar from the surrounding thyroid parenchyma, and it should compress the surrounding thyroid (Fig 289) Very frequently these adenomas reveal central fibrous scarring and not too rarely contain areas of hemorrhage. The Hürthle cell lesion is very frequently cellular and often large



Fig 290—Photomicrograph of boundary between cellular adenoma and normal thyroid. Note difference in appearance between adenoma and thyroid and the presence of a well defined capsule. (×300) (Courtesy Dr Julian Blache Homer Phillips Hospital, St. Louis, Mo.)

Microscopically the simple adenoma (fetal and embryonal) is the most common of all thyroid adenomas and is usually made up of small thyroid follicles which may or may not contain small amounts of colloid (Fig 290) Zones of fibrosis are often present in the center, and evidence of recent or old hemorrhage is common. At times the cells have a trabecular arrangement and are present in anastomosing columns. Because of this pattern some of these lesions are called embryonal adenomas. Considerable variation in the size and shape of the cells may be seen, but these changes, even when they are very prominent, are not necessarily an indication of malignant alteration

Hürthle Cell Adenoma.—Microscopically this relatively rare but distinct type of adenoma is made up of large cells with abundant granular pink cytoplasm. Nuclei are well defined with relatively prominent nucleoli. These cells are fre

quently arranged in solid masses and at times in columns. Small follicles with a small amount of central colloid may be seen Mitotic figures are infrequent (Gardner)

Gross and Microscopic Evidence of Malignant Change in an Adenoma

Gross Evidence.—All of the adenomas previously described may become malig nant, the signs of malignancy including both gross and microscopic changes In order to call a given adenoma malignant, it is important first to note whether or



Fig 291—Drawing of a large encapsulated follicular adenocarcinoma of the thyroid with gross evidence of vein invasion. This finding is unusual in our experience.

not there has been any infiltration of the tumor through the capsule into the sur rounding thyroid. Extension into the capsule alone does not necessarily indicate malignancy but further development into the thyroid, or even more pertinent, beyond the thyroid parenchyma into the surrounding perithyroid tissues, indicates a cancerous growth. It is important also that the surrounding large veins be ex amined, for in rare instances the tumor may directly invade, block and distend these veins (Fig 291) On section grayish white tumor will be seen ballooning out and distending their lumen.

Microscopic Evidence.—Given a true adenoma of the thyroid it is important that multiple sections be cut in the region of the capsule. At least five or six

sections should be taken and stained not only in the conventional fashion but also with any one of the several stains which bring out the integral parts of the blood vessel wall to indicate the presence or absence of blood vessel invasion. Sections through the capsule may show embedded tumor cells but this may simply represent fibrous entrapment of the adenomatous tumor cells and not necessarily be evidence of malignancy. Invasion of the tumor through the capsule into the surrounding parenchyma is definite evidence of malignant change. Tumor cells often seen lying free within the lumina of small veins *are not evidence of malignant change*. These tumor cells must be attached to the vein wall and a true tumor thrombus be present before a diagnosis of cancer can be made.

Frozen Section

Since the nature of a thyroid tumor cannot be determined clinically, surgical investigation is indicated. The most common reason for exploration is the presence of a dominant apparently single nodule in the thyroid in a patient without clinical signs of toxicity. At the time of exposure of the thyroid it is often discovered that there is not one nodule but multiple nodules and that a diagnosis of nodular nontoxic goiter is obvious. In some instances the patient will have a pathologic process that invades the contiguous muscle. Frozen section of this muscle will then show invasive adenocarcinoma. In other instances there may be enlarged lymph nodes in the region of the isthmus or in the region of the lymphatic drainage of the thyroid. Frozen sections of such nodes may show metastatic carcinoma. If exploration of the neck in the region of the thyroid is unrewarding the surgeon must then turn his attention to the single nodule. This nodule, if small, can be removed with a margin of normal thyroid, but in most instances its removal implies hemithyroidectomy. This nodule *must never be enucleated* for if it is cancer it will be implanted throughout the tissues of the neck. After removal of the nodule the pathologist sections it and does a frozen section. The diagnosis will invariably be one of three things: a nodule of an adenomatous goiter, a true benign tumor, or a cancer. The microscopic diagnosis will determine the therapy. Any pathologist with a good background in surgical pathology should have no difficulty in making a definitive diagnosis in over 90 per cent of instances.

Difficulties will arise under the following circumstances. If the patient has a pronounced hyperplasia of the thyroid gland it may even infiltrate the surrounding muscle. Under these circumstances, however, the surgeon will be well aware of the clinical diagnosis and will not call for a frozen section. If the patient has had previous surgery on his thyroid it will be possible for the surgeon to implant normal thyroid tissue at a considerable distance from the thyroid and it may therefore be confused with metastatic carcinoma. There should be no difficulty in the diagnosis of such diffuse lesions as Hashimoto's disease and chronic granulomatous thyroiditis. Undifferentiated carcinoma will be an obvious diagnosis, and the diagnosis of papillary carcinoma will be a certainty particularly if *psammoma bodies* are seen (Fig. 292). The greatest difficulty will occur, of course, in the well differentiated follicular carcinoma. This type of neoplasm is rare and usually there will be evidence of infiltration of surrounding structures or true venous thrombi to support the diagnosis.



Fig 292.—Classic psammoma bodies occurring as small calcific spherules within the stalk of the well-differentiated papillary carcinoma. (×180) (W U neg 54 134A.)

Malignant Tumors

Papillary Adenocarcinoma.—We believe that papillary adenocarcinoma is cancer from its inception and we seriously doubt the existence of benign papillary cystadenoma. Papillary adenocarcinoma metastasizes in a high percentage of instances through the lymphatics. Metastasis through the blood stream by vein invasion is infrequent but if it occurs distant metastases to lungs and bone will appear

Grossly the primary tumor may be extremely small and may be evident only as a grayish white poorly delimited area. At times it is only found on microscopic section. Our smallest primary tumor measured 4 mm. Consequently very complete sectioning of the glands may be necessary to demonstrate the primary tumor The larger lesions have a papillary character that can be discerned grossly (Figs. 293 294 and 295) The involved lymph nodes retain their original shape and may not be enlarged, but very frequently the architecture is completely obliterated and replaced by grayish white tumor tissue. Involved nodes may not be palpable because they are not enlarged and their consistency does not differ from that of a normal node. This finding is well substantiated by Frazell who found that in 67 patients who had no evidence of disease within the lymph nodes prior to neck dissection 41 had involved nodes (61 per cent)

Microscopically the tumor in the thyroid and that in the nodes usually have a similar microscopic pattern, but the regularity of the architecture may vary



Fig 293—Gross photograph of a lobe of the thyroid completely replaced by a papillary adenocarcinoma. The small mass represents complete replacement of a lymph node (W U neg 50-304)

Fig 294—Gross photograph of a papillary adenocarcinoma of the thyroid measuring about 1 cm. The patient had extensive lymph node metastases and naturally the primary tumor could not be felt. (W U neg 52 3904)



Fig. 295 —Gross photograph of a papillary cystadenocarcinoma. This has been slightly enlarged so that the papillary character of the tumor can be seen. (W U neg 51 5865)

Figs. 296 and 297 —Photomicrographs to demonstrate at low power the papillary character of the tumor and at high power the layering of the cells in the individual papules. Fig 296 Low power (W U neg 48-5637) Fig 297 High power (W U neg 48-5641)

from area to area These tumors have a papillary character, but focal areas of follicular cancer also may be present When cancer is present, the individual papillary zones may be multilayered and frequently show marked variation in size and shape (Figs. 296 and 297) Fairly often small calcific spherules (psammoma bodies) may be seen within the epithelial areas arising from the connective tissue of the stalk, evidence that tumor has been present for a long time. Their presence is diagnostic of papillary carcinoma and this fact may be of great practical value in frozen section (Fig 292) (Underwood) These crystalline bodies stain for iron (Johnson)

Papillary Adenocarcinoma—So-Called Lateral Aberrant Thyroid—When a primary papillary adenocarcinoma is small the first clinical evidence of tumor may be the presence of a mass in the neck In the past with complete replacement of a node by tumor the lesion was called lateral aberrant thyroid. If there was evidence of further metastases it was thought that the malignant tumor arose from this lateral aberrant thyroid tissue. When a similar tumor was found in the homolateral lobe of the thyroid, it was thought by some to represent a metastasis from the cervical mass. It is now well recognized that tumors in the neck represent metastatic carcinoma from a primary neoplasm invariably located in the homolateral lobe of the thyroid. King in 1941 analyzed 54 cases and found that practically all of the lesions represented metastatic extensions into deep cervical lymph nodes from primary carcinoma of the homolateral lobe of the thyroid Embryologically if lateral aberrant thyroid tumors are derived from lateral anlagen they should be situated along the tract of the lateral anlagen from the pharyngeal wall to the thyroid. Weller demonstrated that the tract lies between the carotid sheath and the thyroid lobe laterally and in the trachea and esophagus medially As King points out, these so-called lateral aberrant tumors lie superficially or externally to the carotid sheath. If normal thyroid were displaced, it should be found in some of the radical neck dissections performed for other types of carcinoma but King has never seen such thyroid tissue in neck dissections, nor have we ever seen it in the hundreds of dissections done at the Ellis Fischel State Cancer Hospital in Columbia, Mo or at Barnes Hospital in St. Louis, Mo Furthermore, in our experience, in 100 per cent of instances when thyroidectomy was done promptly upon finding a lateral aberrant thyroid (so-called lateral aberrant carcinoma) a primary neoplasm was demonstrated in the thyroid. It should be emphasized that the finding of this primary neoplasm may require extremely careful microscopic study with blocking of the entire thyroid gland and cutting of the blocks at various levels (Wozencraft) Finally if these metastatic deposits are carefully examined, their distribution will be normal for the nodes in that area And moreover if they are cut at various levels a rim of remaining compressed lymphoid tissue of the node can frequently be seen (Fig 298) In the same type of tumor lymphoid tissue is usually absent within the thyroid gland.

Alveolar Type Adenocarcinoma—Alveolar adenocarcinoma occurs much less frequently than papillary cystadenocarcinoma. Grossly it usually forms a single mass within the thyroid which is nonencapsulated and grayish white in color Microscopically this tumor frequently reproduces the pattern of the thyroid and may be extremely well to poorly differentiated In some areas definite acini may

Fig 298 —Photomicrograph of a papillary adenocarcinoma metastatic to a cervical lymph node. (×230.) (W U neg 51-6018)

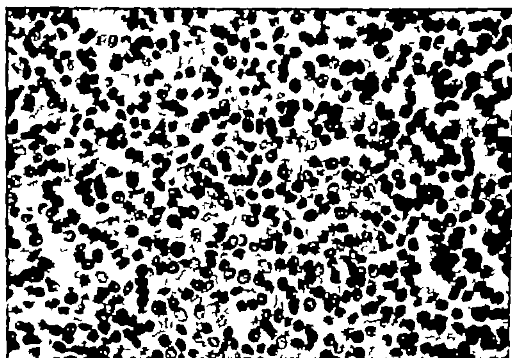


Fig. 299 —Photomicrograph of well-differentiated carcinoma of the thyroid with small uniform cells. (W U neg 48-5642)

be seen, in others small amounts of colloid are present in the center of these acini It may be so well differentiated that a metastasis to, let us say bone may show nothing but tumor and be impossible to differentiate from normal thyroid However there is *no doubt* that clinically it is neoplastic and represents carcinoma Alveolar carcinoma again illustrates the great difficulty there is in diagnosing pathologically well-differentiated tumors of the thyroid When this tumor is restricted to the thyroid itself, it may be identified as carcinoma by the invasion of veins. At times differences in staining and quite marked changes from the surrounding thyroid are present the changes suggesting, but not diagnostic of, carcinoma. This tumor metastasizes frequently to the lungs the bones of the shoulder girdle, sternum skull and large bones such as the ilium. If the primary tumor of the thyroid is small the metastatic lesion may grow slowly and present a mass which pulsates because of its vascularity When x ray reveals a metastatic pulsating lesion the chances are high that it arises from either kidney or thyroid

This is the type of carcinoma which shows a strong avidity for radioactive iodine. The more closely thyroid cancer resembles normal thyroid, the greater the chance for an appreciable uptake. Only a small portion of the papillary carcinomas take up radioactive iodine to any degree. The undifferentiated carcinomas do not take up significant amounts In this well-differentiated alveolar type radioactive iodine may be used as a palliative therapeutic agent when the disease has become disseminated but it does not sterilize metastatic cancer except under the rarest circumstances.

Small Cell Carcinoma.—This tumor grossly involves large areas of the thyroid and frequently invades the surrounding ribbon muscles. Microscopically it is made up of monotonous masses of small cells with very little cytoplasm and with homogeneously staining nuclei (Fig 299)

Giant Cell Carcinoma.—The so-called giant cell tumor is an extremely undifferentiated neoplasm in which there are numerous tumor giant cells It usually widely infiltrates all the surrounding structures including the ribbon muscles the esophagus the wall of the trachea, and even contiguous bones Distant metastases are common but there is often so much obstruction in the air passages that the patients die of respiratory failure. Prognosis in this type of tumor is extremely poor if not hopeless

Rare Tumors.—

Hürthle Cell Carcinoma—This is a rare malignant neoplasm which metastasizes in the same way as other malignant tumors of the thyroid. It reveals its identity by its microscopic pattern large polyhedral cells with abundant eosinophilic granular cytoplasm (Figs. 300-302) The tumor has a fairly regular pattern even in its metastatic foci.

Occult Sclerosing Carcinoma—These rare carcinomas, often found in thyroidectomies done for other reasons were first considered to be of little clinical significance. These adenocarcinomas however, metastasize to regional lymph nodes in at least one third of the cases (Klinck) (Figs 303 and 304)

Squamous Carcinoma—Squamous carcinomas may arise from remnants of the thyroglossal duct. Jaffe believes that metaplasia of normal thyroid epithelium







Figs. 300 to 302.—Hürthle cell carcinoma.

Fig. 300.—Clinical photograph of 44-year-old woman with well-circumscribed thyroid nodule of two years duration. The scar is from an operation done nine years before for hyperthyroidism. (W U negs. 48-4150 and 48-4151.)

Fig. 301.—Gross photograph of the tumor. Note relative circumscription and cellularity. (W U neg 48-4259.)

Fig 302.—Photomicrograph of Hürthle cell carcinoma. Note large cells with prominent cytoplasm. This tumor invaded veins. The patient died with bone and lung metastases six years after surgery. (×625.) (W U neg 52 2872.)



Fig 303 —Photomicrograph of poorly delimited sclerosing carcinoma of the thyroid discovered incidentally at the time of subtotal thyroidectomy for nontoxic nodular goiter (Low power) (W U neg 55-4663)

Fig 304 —Photomicrograph of the lesion shown in Fig 303 Tumor is growing as a follicular carcinoma. (×130) (W U neg 55-4664)

to the squamous type may rarely occur with resulting carcinoma. He has photomicrographs which suggest this change. Squamous metaplasia unrelated to carcinoma may occur in a variety of pathologic states and should not be confused with carcinoma (Klinck)

Plasmacytoma.—Plasmacytoma of the thyroid gland has been reported by Shaw and we have seen one in which there was diffuse involvement of the thyroid without involvement of other organs. In this case a subtotal thyroidectomy was done followed by irradiation to the remaining thyroid (Pinkerton) We have also seen several instances in which plasma cell infiltration was prominent. There was another patient, aged 41, who had tumorlike involvement of the thyroid (300 grams) in which the mass was resected (Heptinstall) This patient had no evidence of disease elsewhere, including the bones. We believe that the changes present were in reality nonneoplastic. The diagnosis therefore should be plasmacytoma or plasma cell granuloma

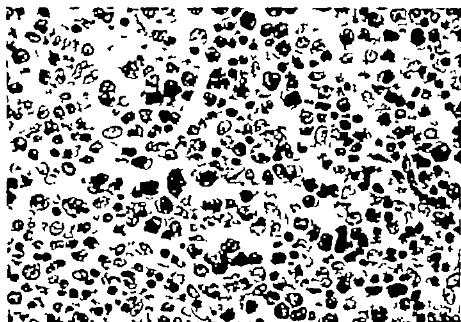


Fig 305 —Photomicrograph of a reticulum cell sarcoma of the thyroid in an adult treated by irradiation therapy Tumor completely disappeared and the patient is living after more than seven years from the date of irradiation therapy (W U neg 50-684)

Lymphosarcoma—True lymphosarcomas can occur but most of these tumors are probably small cell carcinomas which do not respond to irradiation or present characteristic evidence of lymphosarcoma (peripheral lymphadenopathy enlargement of the liver and spleen) We have seen a few radiosensitive lymphosarcomas in one instance the lesion was biopsied and the patient treated by irradiation therapy with seven year survival (Fig 305) Of the eight cases reported by Dinsmore, the entire group died within seven months in spite of surgery and radiotherapy

Fibrosarcomas and Teratomas—Most tumors designated as fibrosarcomas are in reality undifferentiated carcinomas with spindle cells. In a few rare instances true fibrosarcomas have been reported (Zeckwer) Cystic teratomas of the thyroid usually occur in children (Bale) (Fig 306)

It must be remembered that the classification of thyroid tumors is valuable in diagnosing and assessing clinical behavior and treatment in groups of cases. One tumor may be composed of more than one type of neoplasm. We have had the experience of seeing a great variation in types in a single case that came to post mortem examination (Figs. 307 310). Such variation in microscopic pattern may have some bearing on the differences in uptake of radioactive iodine in the metastases.

Metastatic Carcinoma.—In widely disseminating carcinomas, invasion of the thyroid may occur via the blood stream. We have seen metastases from melanocarcinomas, carcinoma of the kidney, cervix, breast, and lung. Carcinomas of the larynx sometimes invade the thyroid secondarily. In 1,000 consecutive autopsied cases of disseminated carcinomas reported by Abrams the thyroid was involved in 19.



Fig. 306.—Cystic teratoma of the thyroid in a 4-week-old white male. Clinically the lesion was considered to be a congenital goiter. (W U neg 54 1492.)

CLINICOPATHOLOGIC CORRELATION

Carcinoma of the thyroid is still an infrequent neoplasm. If it is obviously clear clinically it is practically never curable. It does not occur except coincidentally with hyperthyroidism. It is associated with nodular nontoxic thyroid in an appreciable number of cases, and there is a real risk of its presence in a single nontoxic nodule. The proper treatment of such single nodules is important in the cure of cancer of the thyroid.

The classification of thyroid cancer has merit for there is a rough parallelism between the well-differentiated forms and prognosis. It is fortunate that a high percentage of thyroid cancers are well differentiated (Meissner). It must be re-



Figs. 307 310 —*(See opposite page for legends)*

ed that in the evaluation of any group of thyroid cancers, the papillary carcinoma and the well-differentiated follicular type may have an exceed long clinical course It is not rare for instance in a papillary cancer, for tases to be present in lymph nodes or even the lungs for over five years, we of one case of papillary carcinoma which has now existed for a twenty year l It is important that the physician realize that thyroid cancer can occur young patient and it is not a rarity in children (Winship) Anaplastic can es not occur in children (Hayles) The only possible method of cure is by iate surgery Well planned irradiation and radioactive iodine are only pallia gents (Fitzgerald)

he common papillary carcinoma deserves special comment because of its controversial aspects. The long natural history of the disease makes evalu of any form of treatment difficult if not impossible It has now been shown his lesion has either multiple foci of origin within the thyroid or it originates y and extends widely through the thyroid by means of the abundant lym network In surgical specimens the incidence of multiple areas of involve in the gland is at least 80 per cent (Russell) Hemithyroidectomy therefore, al removal of a nodule will not remove the cancer in over half the cases. p recurrence may appear in these cases where incomplete surgery has been (Rundle) However some surgeons believe that total thyroidectomy carries it too much morbidity (hypoparathyroidism and severing of recurrent laryn nerves) Frazell has demonstrated that in patients with papillary cancer at 60 per cent will have involved regional lymph nodes even though they are palpable. This would appear to be an excellent argument for elective dis n If nodes are palpable, the chances of their being involved are almost 100 ent.

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Figs 307 310 — Photomicrographs to demonstrate the variation possible in a primary ld carcinoma and its metastases. Such variation may explain differences in uptake of ective iodine.

Fig 307 —The primary tumor is highly undifferentiated and could be designated as ant cell type (×500) (W U neg 50-3342)

Fig 308 —Metastasis to the kidney This could be called the follicular type of car a of the thyroid. (×400) (W U neg 50-3341)

Fig. 309 —Metastasis to the hilar lymph nodes. This could be designated as squamous oma of the thyroid. (×400) (W U neg 50-3340)

Fig. 310 —Metastasis to the lung This could be called papillary carcinoma of the id. (×400) (W U neg 50-3343)

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pter 9

GASTROINTESTINAL TRACT

ESOPHAGUS

)PSY, EXFOLIATIVE CYTOLOGY

Exfoliative cytology for lesions of the esophagus is of value in those instances :re biopsy is not possible or is difficult At the time of esophageal biopsy speci is for cytologic examination can also be obtained. In severe esophagitis false itives have been reported (Johnson) It is important that biopsies be fixed nediately and sectioned at various levels for at times only a few collections of ignant cells may be present

NIGN LESIONS

otic Ulceration

Peptic ulceration of the terminal third of the esophagus almost always occurs h hiatus hernia. Belsey believes that the ulceration occurs in the herniated tric mucosa. The defect in the cardiac sphincter mechanism allows hydro-

chloric acid and pepsin to produce ulceration fibrotic contracture, and esophageal shortening A congenital short esophagus only rarely occurs. Contraction occurs secondary to the inflammation (Allison) There is some difficulty in determining exactly where the esophagus terminates and the stomach begins, but the esophagogastric mucosal junction is the logical boundary The ulceration occurring with esophagitis is well delimited. There are fibrous bands radiating from it, and the lumen of the esophagus is narrowed On cross section the muscle may be partially replaced by dense fibrous tissue (Fig 311) The esophagitis may be associated with acute ulceration chronic ulcer, and healed fibrotic stenosis (Allison) Microscopically there is an ulcer associated with chronic inflammation and fibrosis. This type of ulcer does not become malignant. Clinically it may simulate a carcinoma of the terminal third of the esophagus but the biopsy will be negative and cure can be effected by surgical resection.



Fig. 311 —Specimen of a resected esophagus demonstrating chronic peptic ulceration of the terminal third of the esophagus with deep penetration of the ulcer (W U neg 49-3670)

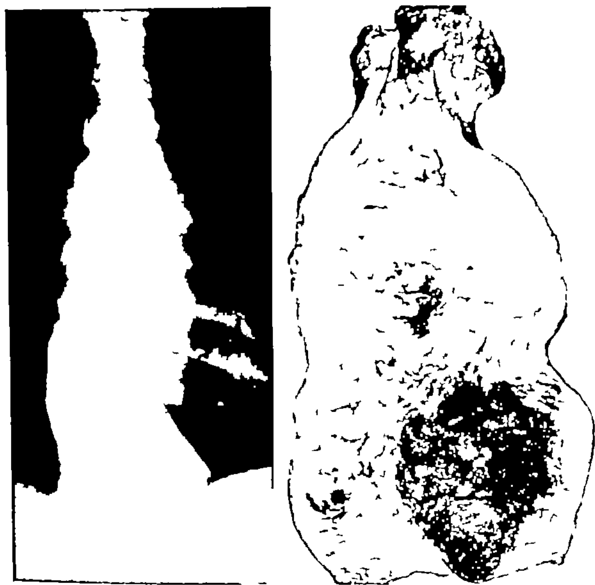
Lye Strictures

Lye strictures of the esophagus usually occur at the anatomic points of constriction. They are most common at the level of the bifurcation of the trachea (Kiviranta) If lye stricture is well established the only possible method of cure is surgical resection (Bosher Burford) Carcinoma of the esophagus may develop at the site of a lye stricture (Bigelow)

Achalasia

Achalasia (cardiospasm, megaesophagus) is related basically to emotional stress (Wolf) Megaesophagus may be due to a failure of the cardiac sphincter to open when peristaltic waves conveying food through the esophagus reach it

(Puppel) Supporting this theory are degenerative changes in the ganglion cells of Auerbach's (myenteric) plexus (Rake) In the early stages this process is reversible but with the passage of time chronic inflammation and ulceration supervene and fibrotic stricture results Rarely, cancer is associated with long standing achalasia (Figs 312 and 313)



Figs. 312 and 313 —Roentgenogram and gross specimen of achalasia (mega-esophagus) with superimposed area of ulcerating squamous carcinoma. (W U neg 49-3478)

Heterotopic Gastric Mucosa

Heterotopic gastric mucosa can occur at any point in the esophagus but appears most frequently in the postericoid region (Schridde, Rector) We have seen it produce a filling defect in the mid portion of the esophagus (Bosher) (Fig 314) It may produce signs and symptoms suggesting a malignant neoplasm. Grossly the surface resembles gastric mucosa (Fig 315) Frequently the lesion is sharply delineated, and the difference between this epithelium and the normal stratified



Fig. 314 Esophagogram ...

epithelium is apparent At times ulceration occurs Microscopically this gastric mucosa is usually made up of long typical gastric glands which are almost entirely mucin secreting in nature (Fig 316) The specific cells of the mucosa are rare There often is excessive inflammatory reaction which coupled with the presence of the glands may cause an erroneous diagnosis of adenocarcinoma. We have seen a single instance of carcinoma arising in heterotopic gastric mucosa in which normal lining squamous epithelium was present both proximal and distal to the lesion It was arising from mucous glands (Foraker)

Diverticula, Enteric Cysts

The diverticula appearing in the upper portion of the esophagus are the result of outpouching esophageal mucosa at points of weakness in the wall of the esophagus In the upper portion of the esophagus the impairments are at the junction of the pharynx and esophagus They are more properly designated as diverticula of the hypopharynx and are classified as pulsion diverticula They occur at this point because of the relationship between the inferior constrictor muscle and the obliquely passing fibers of the cricopharyngei as they descend upon the posterior wall of the esophagus to become longitudinal (Lahey) In the lower third of the esophagus and in the region of the hilum of the lung inflammatory lymph nodes (usually tuberculous) become firmly attached to the esophagus and diverticula may form as a result of traction these are called traction diverticula. Just above the diaphragm so-called epiphrenic diverticula of the pulsion variety have been reported rarely (Janes) The outpouchings are false diverticula and contain mucosa submucosa and often muscularis mucosae They are lined by squamous epithelium and may be associated with considerable inflammation Complications may include obstruction infection with perforation and mediastinitis hemorrhage and even carcinoma Enteric cysts have been reported (Rosenak)

Congenital Defects

In a 3 week-old embryo the esophagus is an annular constriction between the pharynx and the stomach With growth of lung buds and elongation of the neck it becomes tubular At first the cephalad portion of the esophagus and trachea form a single channel Later a septum grows in and separates them. Various types of defects persist, the commonest being atresia with fistulous connection between esophagus and trachea at the level of the tracheal bifurcation or at the level of the right main stem bronchus. In this deformity the hypertrophied dilated upper portion of the esophagus ends blindly at varying distances below the larynx The lower portion of the esophagus usually communicates with the trachea about 0.5 cm. above the bifurcation (Plass) Striated muscle is present in the upper esophagus and absent in the lower (Keith) Tracheal structures are often found in the fistulous end of the lower segment of the esophagus (Rosenthal) There can also be defects of the esophagus alone, congenital narrowing or shortening of the whole esophagus stenosis of the lower or upper end, or an occluding diaphragm of mucous membrane At the present time 75 per cent of infants with atresia of the esophagus and tracheoesophageal fistula are being treated success

fully on the Thoracic Surgical Service at the Barnes Hospital (Burford) The tracheoesophageal fistula is closed, and esophageal continuity established (Haight)

TUMORS OF THE ESOPHAGUS

Leiomyoma and Leiomyosarcoma

Of the 200 benign tumors of the esophagus that have been reported, the leiomyoma is the most common (Totten) It occurs much less frequently than carcinoma. At times these tumors are multiple (Rose) Grossly they form well-defined masses arising from the smooth muscle in the wall of the esophagus. If they grow inwardly, they encroach upon the mucosa and may even ulcerate it and form a



Fig 317 —Epidermoid carcinoma of the terminal third of the esophagus demonstrating well delineated ulcer with central ulceration. (W U neg 51 1200)

well-defined mass which on cross section is grayish white in color In the terminal third of the esophagus leiomyomas can encircle the entire wall and constrict it (Harrington) Microscopically they have the characteristics of a benign smooth muscle tumor Under rare conditions they become malignant and are designated as leiomyosarcomas. Local resection or enucleation of leiomyomatous tumors is usually successful (Lewis)

Epidermoid Carcinoma

Carcinoma of the esophagus occurs most frequently in men over 50 years of age. Rarely it is associated with a benign stricture (Benedict) or with achalasia (Bersack), but it is not related to leukoplakia of the esophagus (Figs. 312 and 313) In the gastrointestinal tract this tumor is second in frequency only to carcinoma of the stomach and large bowel. It can occur in any portion of the esophagus, but it is most common in the middle and lower third. In about 75 per cent of in

carcinoma of the esophagus forms well-differentiated cells and grows slowly. Failure to cure carcinoma of the esophagus is based on the growth factors and spread of the neoplasm. The esophagus has no serosal surface, so tumor quickly spreads



Figs. 320 and 321.—Gross photograph of squamous carcinoma of the lower third of the esophagus invading the stomach and photomicrograph which shows the peripheral margin of the tumor. This is a zone of epidermoid carcinoma in situ. (Fig. 320 W U neg 49-6534. Fig. 321 ×200 W U neg 50-2976.)



Fig. 322.—Gross photograph of the resected segment of the esophagus at the junction of the upper and middle thirds. There was previously a large area of ulcerating carcinoma at this point in the organ. The carcinoma was heavily irradiated. The ulceration disappeared and was replaced by smooth mucosa. However after many sections there were still residual carcinoma in the esophagus and tumor in the regional lymph nodes. This specimen illustrates the value of irradiation as a palliative procedure (W U neg 49 1328)



Fig 323.—Gross photograph of a polypoid carcinosarcoma of the upper third of the esophagus occurring in a 66-year-old man There were no metastases and the tumor had not extended through the wall. (W U neg 52-3827)

through the muscle to the periesophageal tissues. The esophagus is also abundantly supplied with lymphatics at all levels which may transport tumor below the diaphragm or upward into the cervical lymph nodes. Unexpected extension of the tumor may be found in careful examination of surgical specimens. We subserially cut a surgical specimen of a carcinoma of the esophagus and found tumor 5 cm. above and 7 cm. below the gross limits of the tumor This submucosal extension could not be seen or felt grossly Burgess studied 15 specimens of carcinoma of the esophagus microscopically and found intramural spread from 1 to 4 cm. beyond the gross limits of the tumors. In one of our specimens epidermoid carcinoma in situ of the epithelium was found apart from the primary tumor supporting the concept of multiple foci of origin In the small percentage of resectable carcinomas cures are infrequent because of early metastases (Sweet) When operative removal of an epidermoid carcinoma of the esophagus is performed, frozen section of tissue at the levels of transection will help establish the adequacy of the resection. Considerable palliation is achieved by well planned irradiation and cures have been reported by this form of treatment (Buschke) (Fig 322) Radiation therapy is best indicated for carcinoma of the upper third of the esophagus, and surgery for the lower third cancer of the middle third responds poorly to both methods of treatment.

Rare Tumors

Other malignant tumors of the esophagus are a rarity Stout has reported a carcinosarcoma, and we have recently seen one in a 66-year-old man (Fig 323) We have also observed metastatic carcinoma involve the nodes in the region of the esophagus and secondarily invade it (Thoreson) An example of primary melanocarcinoma of the esophagus has been reported (Boyd)

It is common for a primary carcinoma of the stomach to invade the terminal third of the esophagus. In such instances the biopsy demonstrates adenocarcinoma instead of epidermoid carcinoma.

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STOMACH

METHOD OF EXAMINATION

Gross Examination

The stomach lesions submitted to the surgical pathology laboratory are either partial or complete resections of the stomach which should be quickly placed in fixative because autolysis takes place rapidly. It is useful to pin the specimens on cardboard in a 10 per cent formalin solution. After fixation is complete, the sections can be taken carefully and all lesions can be diagrammatically recorded. If it is of interest to take sections of the entire mucosal surface, a thin strip of gastric mucosa can be lifted from the underlying muscle and then rolled up into a compact ball, fixing the entire tissue with a pin and placing it in 10 per cent formalin. In this fashion an entire lengthwise section of the mucosal surface of the stomach can be taken (Hebbel).

In ulcerated lesions complete transection of the lesion from one end to the other can be made if necessary. It is important to obtain sections from all areas of the stomach to show any variable pathology which may be present. With tumor it is important to take sections of the area of transition between involvement and noninvolvement. If a carcinoma is located close to the pylorus it is imperative that a section be taken through the pylorus including the duodenum. Both ends

of the resected specimen should be sectioned and examined for tumor Lymph nodes should be carefully dissected and placed in separate bottles for identification of specific lymph node groups

Exfoliative Cytology

Exfoliative cytology in debatable lesions of the stomach has not been exploited to its fullest practical extent There are numerous recent reports that indicate the accuracy of the method Cromer has shown that exfoliative cytology is even more accurate than roentgenograms (Table 13) In the group of cases shown by this Table there were 4 patients in whom the x ray diagnosis was benign disease or was equivocal in nature. All 4 patients proved to have cancer at the time of gastric resection Middleton found that the use of a brush or mucolytic agents does not improve the accuracy of the method The best results were obtained in patients in whom there was careful preparation and thorough gastric lavage was done with isotonic saline solution Raskin has also obtained an extremely high degree of accuracy in both the esophagus and the stomach (Table 14) *Cromer states the value of exfoliative cytology succinctly* "*It appears to us that* the circumstances in which gastric cytology is most useful are to substantiate the clinical impression of a benign lesion to enhance the clinical impression of a malignant lesion and on occasion, to diagnose an early unsuspected gastric cancer Schade has identified several very small cancers of the stomach by cytology The radiographic studies in these cases were completely negative or nondiagnostic.

TABLE 13 EXFOLIATIVE CYTOLOGY IN LESIONS OF THE STOMACH*

GROUP	PATIENTS STUDIED	OVER ALL ACCURACY OF CYTOLOGIC STUDIES		OVER ALL ACCURACY OF ROENTGENOGRAM	
		NO	PERCENTAGE	NO	PERCENTAGE
Benign Lesions	151	149†	98 7	(24.5 per cent classified as probably malignant or malignant by roentgen study)	
Malignant Lesions	41	29‡	76 0	(67.5 per cent classified as malignant and 20 per cent as suspicious)	

*From Ross J R. McGrath, J M Cromer R. E Rohart, R. R. and Middleton M Gastroenterology 34: 24 33 1958

†Of the remaining two cases, one was called suspicious and the other malignant.

‡An additional two cases were called suspicious.

TABLE 14 RESULTS OF THE CYTOLOGIC METHOD* APRIL 1955 TO DECEMBER 1958

	TOTAL NO OF PATIENTS EXAMINED	PROVED BENIGN	NEG	FALSE POS	PER CENT ACCURACY	PROVED MALIG	POS	FALSE NEG	PER CENT ACCURACY
Esophagus	163	93	91	2	97	70	67	3	95
Stomach	1 032	889	885	4	99	143	136	7	95

*From Raskin H. F., Kirsner J B., and Palmer W L. Exfoliative Cytology of the Gastrointestinal Tract, in Jones F A. (editor): Modern Trends in Gastroenterology ed. 2 London, 1958 Butterworth & Co. Figures corrected to December 1958 by Dr Howard F Raskin

Gastroscopic Biopsy

Gastroscopic biopsy has been used by Benedict in the differential diagnosis of chronic gastritis diffuse carcinoma, and lymphoma. He has correlated the biopsy findings with the x rays and the surgical specimens. A positive biopsy is of great value (Fig 324) for it influences definitive therapy a negative biopsy is of limited value and there are areas in the stomach inaccessible to biopsy Gastroscopic biopsy in the United States has not been exploited to its fullest extent (Atkins)

Frozen Section

Frozen sections of lesions in the stomach and the immediate areas may be helpful in determining the operative procedure. Furthermore frozen section of lymph nodes or of peritoneal implants far from the primary abdominal cancer may reveal metastatic carcinoma and so influence the type of operation. With perforation of the stomach due to an ulcer particularly in an older person a frozen



Fig 324 — Photomicrograph of gastroscopic biopsy of a well-differentiated adenocarcinoma. (×390) (W U neg 52 1631) (Slide contributed by Dr Benjamin Castleman and Dr Edward Benedict, Massachusetts General Hospital Boston Mass.)

section of the ulcer should be done if it is carcinomatous, gastric resection is indicated. In still other instances the radiologist may describe a lesion which the surgeon is not able to identify frozen section of generous biopsies of the questionable area shown by radiograph may be diagnostic. In a few instances linitis plastica has been diagnosed on frozen section but it is usually extremely difficult because of the excessive connective tissue present A diagnosis of lymphosarcoma can also be made. The benign character of huge ulcers of the stomach can be shown by frozen section. In 34 giant ulcers of the stomach collected by Shoulders 26 were benign. When an ulcerated lesion of the stomach is found by the surgeon

he must weigh the value of frozen section against the possibility of implantation of cancer by multiple biopsies of the ulcer If the debatable ulcer is situated in the mid portion or the distal half of the stomach and there is no evidence of neoplastic spread beyond the stomach removal of 70 to 80 per cent of the stomach, the greater and lesser omenta and the spleen with its hilar group of lymph nodes should be done without gastrotomy and biopsy The removal of the omenta and spleen by the experienced surgeon does not increase significantly the magnitude of the gastric resection which would be done if the ulcer were known to be benign On the other hand an ulcer in the juxtaesophageal area has a greater likelihood of containing cancer In this area surgical therapy varies radically according to the nature of the ulcer In this area specifically biopsy and frozen section are necessary, and the risk of spread of cancer by gastrotomy and biopsy must be taken The latter situation is encountered rarely

NONNEOPLASTIC LESIONS OF THE STOMACH

Heterotopic Pancreas

In 215 cases of heterotopic pancreas in the stomach reported by Palmer 120 were found at the time of operation. Grossly these lesions may form a hemi spheric mass a symmetrical cone or a short cylindrical nipplelike projection. About three quarters of them occur in the submucosal layer and about one seventh in the muscular layer On section they grossly resemble normal pancreas. In the gross pattern in which a nipplelike projection is formed single or multiple ducts may empty on the surface This pancreatic tissue is usually made up of lobules often with few or no islets. Brunner s glands may also be present. We have seen two carcinomas which we thought arose from heterotopic pancreas. We have seen examples of the lesion described by Stewart as adenomyoma. This focal lesion shows glands of the intestinal type Brunner s glands and myomatous proliferation

Hypertrophy of Pylorus

Hypertrophy of the pylorus occurs predominantly in children. Usually no sections are submitted because cure is effected by a longitudinal division of the muscles (Ramstedt procedure) In the adult, however it may occur as an idiopathic finding (80 per cent in males) We agree with Lumsden that this is an extremely rare condition unless it is associated with some other abnormality Radiographically and clinically a tumor may be suspected and in rare instances the stomach has been resected under the erroneous impression of the presence of a neoplasm. Grossly and microscopically all that is found is the prominent hypertrophy of pyloric muscle which ends abruptly at the duodenum. Chronic gastritis is usually present (Hobson)

Gastritis

Gastritis is rare in patients under 30 years of age, and severe gastritis is uncommon until the age of 50 Antral gastritis occurs uniformly in duodenal and gastric ulcers. Usually gastritis in duodenal ulcers does not occur in the body of the stomach, but such changes are common with gastric ulcers. Pangastritis may be associated with carcinoma of the stomach although there are cases in which

the gastric mucosa is perfectly normal Also the severity of the gastritis is often proportional to the extent of the carcinoma (Hebbel) While it is apparent that duodenal ulcer is preceded by antral gastritis and duodenitis (Konjetzny) there is no proof that carcinoma of the stomach develops on such a basis. Mucosal changes in the stomach may be secondary or coincidental to the presence of carci





Fig 325—Gross photograph of extreme polypoid gastritis which was radiographically confused with carcinoma. (From Bartlett J P and Adams W E. Arch. Surg 60: 543 1950)

Fig. 326.—Photomicrograph demonstrating plicated prominent folds of the stomach mucosa. (Low power) (From Bartlett J P and Adams W E. Arch Surg 60: 543 1950)

noma. Infrequently gastritis, particularly in alcoholics may give rise to massive hemorrhage (Welch)

Grossly gastritis may show a thinning and smoothness of the mucosa. At times these changes are diffuse but often they are patchy Microscopically the diagnosis of gastritis depends primarily on the epithelial alterations which consists of dedifferentiation of normal epithelium resembling the intestinal type. There is also cystic dilatation of the glands and the specific cells of the stomach disappear Morson has studied the incidence and extent of intestinal metaplasia and found it greatest in stomachs removed for carcinoma, least in those with duodenal ulcer and with cases of gastric ulcer taking an intermediate position. Furthermore, the incidence and extent of intestinal metaplasia is greater in cancerous than in non cancerous stomachs. Morson also described 12 gastric polyps with intestinal like epithelium arising apparently from such changes in the gastric mucosa. There are other additional changes such as increased submucosal fibrous tissue, infiltration of cells (plasma lymphocytes, mononuclears) in the submucosa and a great predominance of lymphoid tissue which should not be confused with lymphosarcoma. In *pernicious anemia* there is thinning of the mucosa in the fundus and body of the stomach. In the fundus parietal and chief cells disappear and the gastric mucosa is replaced by mucus secreting cells often of atypical gland type (Cox) The pyloric zone remains unchanged. The above changes are specific for pernicious anemia. Carcinoma occurs with increased frequency in patients with pernicious anemia Schell stressed that all stages of transition from benign to malignant epithelium can be seen. When cancer appears it is often multicentric in origin fundic in location and has a polypoid form.

Giant hypertrophy of the gastric rugae is a rare condition first described by Menetrier in 1888 under the term polyadénomes en nappe. It has also been designated as giant hypertrophic gastritis (Bartlett) (Figs 325 and 326) Radiographically and grossly it can be confused with lymphosarcoma and cancer Kenney reported 20 cases, 3 of which had multiple adenomas of the endocrine system.

Peptic Ulceration

Peptic ulceration occurs in the stomach and duodenum, as a marginal or jejunal ulcer after gastrojejunostomy (Wright) in association with a Meckel's diverticulum and in the lower third of the esophagus. Such ulceration occurs in the presence of hydrochloric acid. The physiologic mechanisms in the pathogenesis of peptic ulceration has been extensively studied by Dragstedt. This information is presented well by Harkins.

Acute ulceration of the stomach is a common finding at autopsy and is usually a terminal event. This acute ulceration may occur in any debilitating illness and may result from the presence of an extensive infection or may occur when tubes are passed into the stomach If the ulcer involves only the mucosa, it will heal completely but if part of the muscle is destroyed, it is replaced by fibrotic tissue leaving a depressed pit *Chronic ulceration* of the stomach is much less common occurring mainly along the lesser curvature (so-called magenstrasse) A

benign ulcer however, can occur at any point within the stomach. Chronic ulcers of the stomach are most common along the lesser curvature but occur with varying frequency in other locations. The specific identification of whether a given ulcer is benign or malignant by radiographic examination carries with it a definite

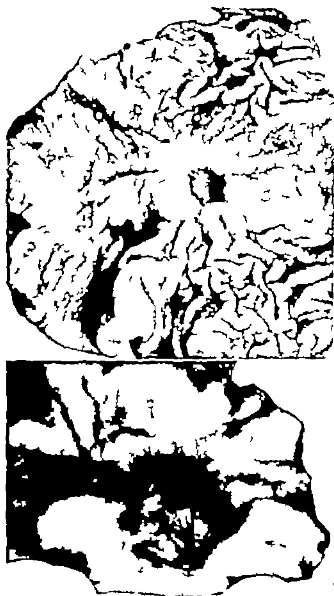


Fig 327 —Gross photograph of a sharply demarcated benign chronic ulcer of the stomach with the converging folds of the stomach mucosa extending right to the margin of the ulcer (W U neg 50-1989)

Fig 328 —Gross photograph of a chronic ulcer of the stomach showing sharp delineation and fibrous replacement of its base.

possibility of error At Washington University of 191 ulcers 101 were designated as benign or probably benign and 5 of these were histologically proved to be malignant (an error of 5 per cent) Ninety were designated as malignant or probably malignant and 25 proved histologically to be benign (an error of 28 per cent) It is much safer for the patient for a benign ulcer to be called malignant than for

a malignant ulcer to be designated as benign In the past it was considered that a high percentage of all ulcers over 2.5 cm were cancer that about 100 per cent of the ulcers of the greater curvature and about 70 per cent of those in the pre pyloric area were cancer In our experience, these statements have not been proved to be true In 49 ulcers larger than 2.5 cm. only 18 were malignant (37 per cent) and 31 were benign. In 12 ulcers on the greater curvature 6 were benign and 6 were malignant (50 per cent) In the prepyloric zone there were 37 ulcers of which only 8 were malignant (22 per cent) (Elliott) These statistics have great interest but in an individual patient they have only relative value Grossly the benign ulcer of the stomach is sharply delineated The converging folds of the stomach mucosa extend to the margin of the ulcer (Figs. 327 and 328) It has been stated that ulcers 2.5 cm or larger represent carcinoma and that smaller ones are probably not malignant. While this is true as a generalization, it lacks specificity it is common for a small ulcer to be carcinoma and for ulcers as large as 10 cm. to be benign. Grossly it is *impossible* to identify carcinoma in an ulcer which appears benign in about 10 to 15 per cent of the instances. On section of a benign ulcer there is an undermining of the edges with complete fibrous replacement of the wall of the stomach by grayish white scar Proximally the ulcer has overhanging edges the distal edge has sloping borders On the surface of the stomach directly overlying the ulcer there is subserosal fibrosis In the vicinity of the ulceration the lymph nodes may be enlarged. Any unusual marginal prominence of the ulceration with increased nodularity should suggest the presence of carcinoma. The transition of a benign ulcer to carcinoma occurs only rarely and we have had difficulty in finding cases which would withstand critical clinical and pathologic analysis These criteria will be discussed later

Microscopically the surface of a benign chronic ulcer shows purulent exudate and fibrinoid necrosis. Subserosal fibrosis and thick walled vessels are present in the wall of the stomach near the ulcer The deeper layers reveal the organization of the exudate and destruction of the muscle with fibrous connective tissue replacement. The vascular changes are secondary to the ulcer In the healing of a chronic gastric ulcer deep epithelial heterotopia with penetration but without transgression of the muscular wall can occur Such changes can be incorrectly diagnosed as carcinoma (Stewart)

Syphilis

Syphilis of the stomach is an extremely rare entity which radiographically and grossly simulates closely the linitis plastica type of carcinoma of the stomach. In the early stages the stomach feels soft but later on becomes firm. Ulceration first occurs almost invariably in the pyloric portion. The liver may show evidence of syphilis with hepar lobatum or stellate scars. In advanced syphilis the stomach is shrunken to a small size and has a so-called leather bottle appearance there is great thickening of the wall of the stomach and there may be ulceration in the region of the pylorus (Palmer) The serology is positive. These findings warrant exploration and frozen section. If several adequate frozen sections show only chronic inflammation of mucosal and submucosal tissue with diffuse lymphoid

infiltration together with considerable desmoplasia but without evidence of tumor the surgeon should close unless the deformity is great enough to warrant resection (Figs. 329 and 330) In our four cases the gross and microscopic findings were compatible with, but not diagnostic of, syphilis

When a differential diagnosis is necessary and the patient has a carcinoma of the linitis plastica type attempts at surgical extirpation uniformly meet with failure (Saphir) On the other hand, if the patient has syphilis, antiluetic therapy may be of great symptomatic value. Williams has reported gumma and gummatoid lesions with proliferative endarteritis and phlebitis in some of his cases.



Fig 329 —Roentgenogram of stomach with prominent deformity due to syphilis. (W U neg 50-4181)

Fig 330. —Gross photograph of resected stomach. Note prominent deformities and areas of ulceration. The microscopic changes were compatible with but not diagnostic of syphilis. (W U neg 50-4181)

Miscellaneous Rare Conditions

Inflammatory fibroid polyp of the stomach is the best name for lesions previously described under the name eosinophilic granuloma, neurofibroma, and hemangiopericytoma. These lesions are frequently associated in patients having a low level of free hydrochloric acid. In 9 out of 10 of the patients reported by Helwig the lesion was in the pyloric antrum. These lesions are probably not true neoplasms. Gross appearance is somewhat similar to a pyogenic granuloma (Fig 331) Pyloric gastroduodenitis can cause pyloric obstruction. It may be associated with allergic phenomena and extreme eosinophilia. The pylorus and duodenum

are thickened and edematous and all their walls diffusely infiltrated with eosinophils. Angiitis involving small arteries arterioles venules, and veins in the submucosa may also be present (McCune) Tuberculosis has been reported (Clagett)

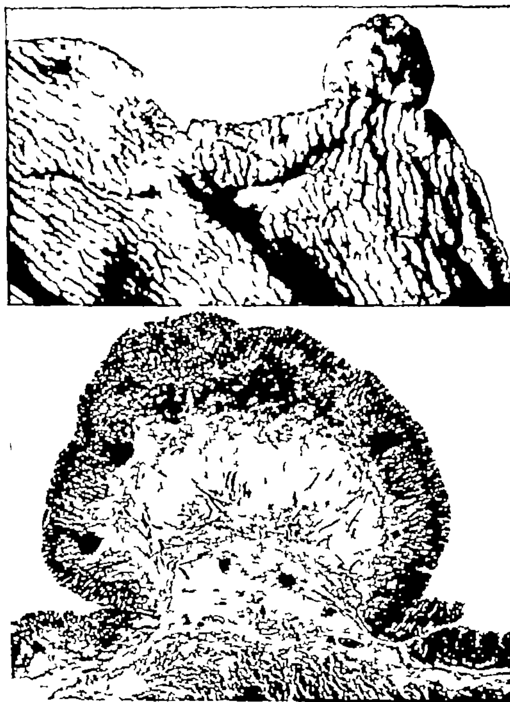


Fig 331 —Inflammatory fibroid polyp of the stomach which was sharply delimited both grossly and microscopically (AFIP 332975) (From Helwig E. B. and Ranier A Surg Gynec. & Obst. 96: 355 1953 By permission of Surgery Gynecology & Obstetrics)

Sirak reported a noncaseating granulomatous lesion of the stomach microscopically suggesting Boeck s sarcoid. The stomach grossly resembled the linitus plastica type of cancer Rarely hemorrhage can occur from perforation of arteriosclerotic aneurysm of gastric vessels within the wall of the stomach (Fig 332) Millard

collected 17 instances of ruptured gastric aneurysm. The etiology was arteriosclerotic and there was a high fatality rate. However 3 were saved by prompt surgical resection. On several occasions we have seen severe gastric hemorrhage take place because of rupture of small submucosal arteries (3 to 5 mm) These arteries were often located high on a lesser curvature. Duplication of the stomach can occur (Goon)



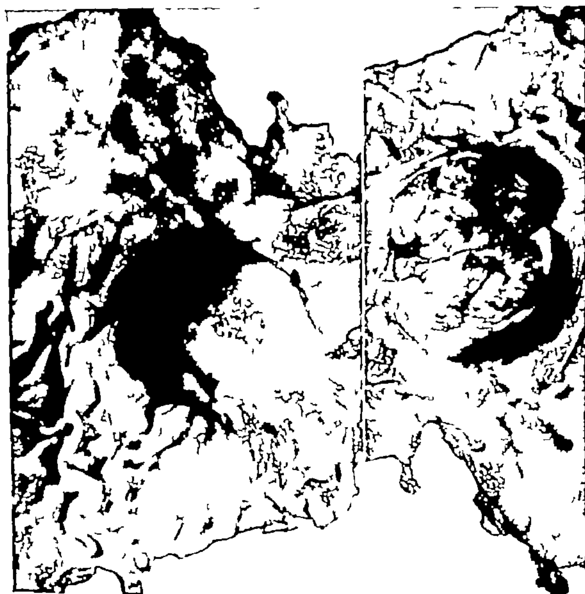
Fig 332.—Photomicrograph of cirsoid aneurysm of a vessel in the wall of the stomach which caused death from hemorrhage. (Low power) (W U neg 52 1831) (Courtesy Dr John Saxton, St. Louis City Hospital St. Louis Mo Case No 14655)

TUMORS

Leiomyomas and Leiomyosarcomas

Leiomyomas are common as an incidental autopsy finding Meissner found 44 leiomyomas in 23 of 50 consecutive autopsies These leiomyomas are often multiple and small and form small well-defined homogeneous nodules. Smooth muscle tumors occur much less frequently clinically than carcinomas but are the most common benign neoplasm of the stomach about 600 cases have been reported. They arise from muscularis mucosae or from the muscular coats of the stomach. They appear most commonly in the region of the pars media (40 per cent) and antrum (25 per cent) (Palmer) They usually are submucosal (about 60 per cent) and grow toward the lumen of the stomach where they make a smooth projection into the lumen (Figs 333 and 334) In time however a central ulceration occurs which may penetrate deeply into the tumor Leiomyomas may grow out from the serosal surface (30 per cent) These smooth muscle tumors may reach

a large size. About 20 per cent occur near the pylorus, but obstruction is rare. On section they usually are well encapsulated with a smooth lobulated or whorled silk appearance An hourglass defect may occur at the cardia or pylorus if the tumor encircles the stomach Areas of hemorrhage may be present If they are



Figs. 333 and 334—Gross photograph of a moderately sized submucosal leiomyoma. On section it shows a rather cellular tumor (Fig 333 W U neg 51 5000 Fig 334 W U neg 51 5001)

excessively cellular or necrotic the presence of malignant change must be considered. Microscopically these smooth muscle tumors show well-differentiated smooth muscle cells with a variable degree of hyalinized connective tissue. They are often misdiagnosed as fibromas or as neurogenic tumors. Prominent variation in the size and shape of the cells is not proof of malignant change. The presence of large numbers of mitotic figures is particularly ominous (Golden) However smooth muscle tumors of the gastrointestinal tract have been known to appear perfectly benign under the microscope and behave as malignant neoplasms clin

ically We have seen 2 such cases. It is therefore possible to underestimate as well as overestimate the malignant potentialities. They do not usually metastasize to regional lymph nodes but spread distantly to the liver and lungs. Giberson reported 40 instances of leiomyosarcoma of the stomach 12 had metastases and there was involvement of lymph nodes in 3 but only by direct extension.

These tumors may be diagnosed roentgenographically because of the smooth outline and central niche in the tumor At the time of operation the pathologist can easily make a gross diagnosis of smooth muscle tumor Although frozen section may help it is often impossible to tell with certainty whether the tumor is benign or malignant Certainly enucleation of the tumor is not adequate. Conservative local resection of the neoplasm and stomach wall is the least that should be under taken. This tumor tends to spread distantly without involvement of lymph nodes therefore wide resection of any lymph node area does not appear indicated. These neoplasms rarely cause signs of obstruction but severe hemorrhage does occur



Fig 335 —Roentgenogram of large polypoid lesion with filling defect in region of pylorus. (W U neg 55-4778)

Fig 336 —Gross photograph of same lesion shown in Fig 335 Subtotal gastric resection demonstrated a polypoid lesion with focal carcinoma. There was no tumor in the stalk and no lymph node metastases. Patient remains well over 2 years. (W U neg 55-4575)

Adenomas

Adenomas of the stomach are less common than smooth muscle tumors. These benign tumors arising from the epithelium of the gastric mucosa occur often in

cases of pernicious anemia (Rigler) These polypoid lesions most frequently occur in the region of the pylorus and can prolapse into the duodenum They are usually rather small but at times attain a considerable size (Figs 335 and 336) Gastric polyposis is a rare but definitely precancerous lesion Pearl reported 37 cases and half of these showed evidence of malignant change We have seen an instance of this lesion with innumerable small polyps together with two early carcinomas (Figs. 337 and 338)

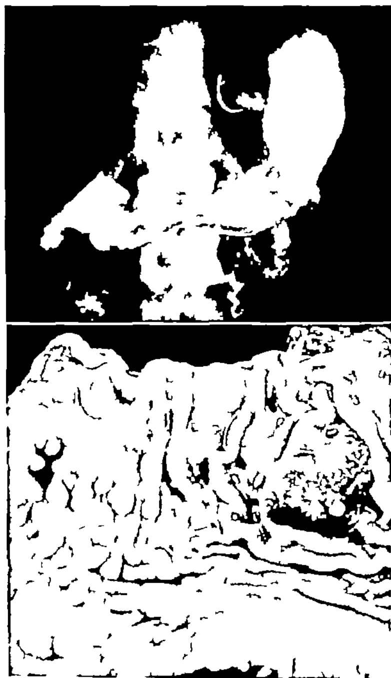


Fig. 337 —Roentgenogram of polyposis of the stomach (W U neg 50-3512)

Fig 338 —Gross photograph of resected stomach. Note innumerable small polyps. There are two larger polyps both of which contain early carcinoma. There were no metastases. (W U neg 50-3395)

Grossly they show all the variations observed in polyps of the large bowel. If they become malignant, areas of firmness or ulceration occur within them. Usually they have a pedicle. If there is no infiltration of the pedicle at operation, partial resection of the stomach is probably all that is necessary. Microscopically these lesions may show the transition from a benign to a malignant tumor (Edwards). It is imperative to remember that if it is not malignant at the time of discovery it has the potential of becoming malignant in the future (Stewart). Although only a small proportion of all carcinomas of the stomach arise from pre-existing polyps they should be resected when discovered.

Carcinoma

The classification of carcinoma of the stomach is of necessity artefactual because practically all of them arise from the mucus secreting cells. In rare instances carcinoma may arise from heterotopic pancreas. The classification of the carcinoma is of value only if it helps in diagnosis or prognosis. Borrman has a system of some merit which shows the gradual gradation between tumors which are fungating and growing mainly within the lumen and those tumors which are deeply invasive and growing through the wall of the stomach. Tumors which evert and grow within the lumen have a much lower incidence of metastasis. Classification can be made as follows:

1. Carcinoma—no specific type (60 to 80 per cent)
2. Carcinoma arising on basis of pre-existing ulcer (5 per cent or less)
3. Superficial spreading type of carcinoma (less than 5 per cent)
4. Carcinoma of the linitis plastica type (less than 5 per cent)

Carcinoma—No Specific Type.—There is wide variation in the gross appearance of carcinomas of the stomach. Unfortunately most of the tumors grow extensively within the stomach, infiltrating a large portion of the stomach wall and secreting variable amounts of mucin. In many instances the tumor spreads to the serosa and involves various node groups. Highly mucinous tumors have a gelatinous appearance.

Carcinoma Arising on Basis of Pre-existing Ulcer.—The criteria for making the diagnosis of carcinoma arising in a pre-existing chronic ulceration should be carefully analyzed. Carcinoma which is found accompanying a peptic ulcer of long duration may be assumed to have arisen from that ulcer but there are many cases of carcinoma of long duration which present only symptoms of ulcer. Stout has 26 cases of which 17 had ulcer symptoms from two to twenty-seven years preceding the development of carcinoma. He felt that it was impossible for a patient to have gastric carcinoma for a period this long.

The diagnosis of carcinoma engrafted on an ulcer should be based on gross and microscopic findings (Table 15). The clinical history can only suggest such a relationship. The criteria are as follows:

1. Rugal folds converge into the ulcer.
2. The ulcer is sharply demarcated.
3. The muscularis on the edge of the ulcer bends sharply upward to fuse with the muscularis mucosae.

4 The base of the ulcer is free of carcinoma and completely replaced by fibrous connective tissue with a broad band of subserosal fibrosis and evidence of obliterative vascular changes.

5 Carcinoma is found on only one margin after subserially sectioning the lesion (Fig 339)

TABLE 15

	EVIDENCE IN FAVOR OF CARCINOMA ARISING FROM PREVIOUS CHRONIC ULCERATION	EVIDENCE AGAINST ORIGIN OF CARCINOMA ARISING FROM PREVIOUS CHRONIC ULCERATION
Authorities Favoring Each theory	Stout Cömöri Newcomb	Mallory Palmer Hebbel
Clinical Data	Long history with peptic ulcer symptoms	A carcinoma may be present for as long as 5 to 10 years (Hebbel Steiner)
Roentgenogram	Typical x ray changes of benign ulcer	10 to 15 per cent error in interpretation of roentgenogram
Gross Appearance	Punched-out ulcer with rugae converging into ulcer	Peptic ulceration occurs secondarily in carcinoma which gives typical gross pattern of benign ulcer
Microscopic Changes	Carcinoma on one margin of chronic ulceration with destruction of entire base base does not contain cancer	Peptic ulceration of carcinoma takes place leaving a ring of carcinoma around border such changes best demonstrated in superficial spreading carcinoma (Mallory)
	Fusion between muscularis mucosae and muscularis represents pre-existing chronic ulceration (Newcomb)	Exceptions to this rule occur
	Deep peptic ulceration rarely occurs in a primary ulcerating cancer	Deep peptic ulceration has been demonstrated in a primary ulcerating carcinoma

In primary ulcerating carcinoma the ulcer does not have steep overhanging edges. Carcinoma is present through the base and the muscle is preserved (Fig 340) Newcomb believes that proof of origin is evident when the muscularis mucosae is adherent to the muscularis However exceptions to this occur It is usually stated that when the base of the ulcer is free of carcinoma the wall is completely replaced by fibrous tissue subserosal fibrosis is present and carcinoma will be found on one or both margins Carcinoma on both margins suggests that peptic ulceration is secondary rather than primary The question arises as to whether peptic digestion of a carcinoma would cause enough destruction of the base of an ulcer to destroy the wall completely We have seen an instance in which carcinoma was present in the margins there was nearly complete replacement of the entire muscular wall by young inflammatory and connective tissue cells. In fact if more time had elapsed the section might have been mistaken easily for carcinoma arising in a chronic ulcer Stout emphasized that in gastric carcinoma it is unusual to find ulceration passing down more than just into the true muscular coat but Mallory has illustrated deep peptic ulceration in a carcinoma.

The number of cases in the literature which will withstand severe pathologic criteria are few Jordan had 111 patients with apparently benign ulcer who were

followed five or more years Two cases of carcinoma developed in that group but these 2 might have had carcinoma for that length of time Mallory and Hebbel have not seen a case. Certainly such malignant change must occur only rarely We have seen personally 4 possible cases over a twelve year period. Stewart's figures showed that in 510 instances of chronic ulcer 51 proved to be cancer (10 per cent) During the interval in which these 51 cancers were found, there was a total of 281 cancers (18 per cent) At Barnes Hospital from 1949 to 1951 61 chronic gastric ulcers were resected 4 of which could be liberally interpreted as showing carcinoma arising on the basis of chronic ulcer (6 per cent) During this same time period in which these 4 cancers were found there was a total of 78 cancers resected (5 per cent) If severe pathologic criteria were applied to these 4 cases one might be accepted as carcinoma arising on the basis of a previous ulcer



Fig. 339 —Gross photograph of an apparently benign chronic ulcer Carcinoma, however was found on one margin. The prominent fold seen at the inferior margin of the ulcer contained carcinoma. EFSCH.

In the past five years we have not seen a single case which we could accept as carcinoma arising from a pre-existing chronic ulcer We are therefore beginning to doubt its existence.

Superficial Spreading Type.—The superficial spreading type of carcinoma forms a serpiginous like ulcer which may reach a considerable size (to 54 sq cm.) (Fig 341) This type of carcinoma of the stomach grows slowly and may involve considerable mucosa without necessarily having muscular invasion. Multiple foci of origin are common (Fig 342) Because of its superficial character the incidence of metastases is low—around 50 per cent (Golden)

Linitis Plastica Type.—The rare linitis plastica type of carcinoma of the stomach presents profound desmoplasia (Saphir) Gross alterations begin in the

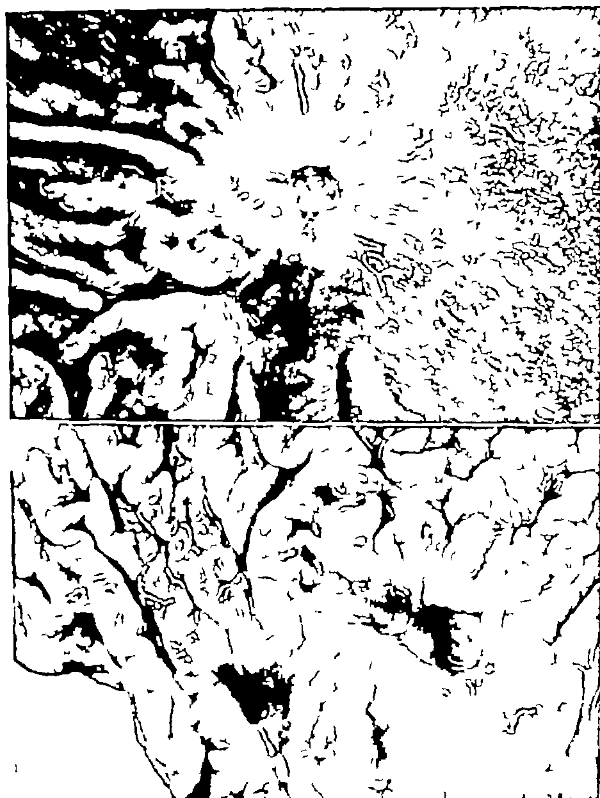


Fig 340 —*A* Illustrates two sharply demarcated benign ulcers with converging mucosal folds. *B* also shows two ulcers which do not look too dissimilar but in reality represent primary ulcerating carcinoma The gross appearance of these ulcers shows the difficulty of determining whether a given ulcer is benign or malignant (W U negs. 54-181 and 54 5518)

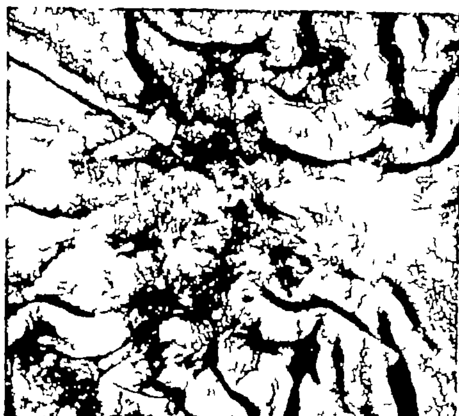
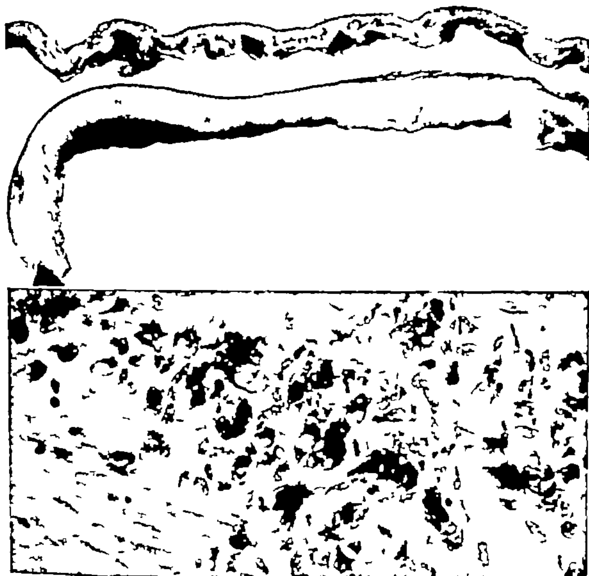




Fig 341 —Gross photograph of a superficial spreading type of carcinoma. The margins are indistinct, and there was no penetration of the muscular coats of the stomach. (W U neg 50-383)

Fig 342. —Photomicrograph of superficial spreading carcinoma. Note complete disorganization of the lining glands. There was no penetration of the muscular coat. (×210) (W U neg 50-6002)

prepyloric area with perhaps some slight superficial ulceration There is evidence of pyloric obstruction as the wall of the stomach becomes thickened (Figs 343 and 344) Sections of the wall of this thickened stomach show hypertrophy of the muscle with a great increase of grayish white submucosal tissue. There are thin fine grayish white areas of tissue infiltrating the muscle, often extending on the serosal surface Lymph node involvement is usually present



Figs. 343 and 344—Gross photograph of a linitis plastica type of carcinoma of the stomach compared with thickness of a normal stomach There is tremendous thickening of the wall with tumor growing in dense fibrous tissue which is well demonstrated in Fig 344 These tumor cells represent small nests of carcinoma cells growing in dense connective tissue (Fig. 343 ×400 W U neg 49 7107 Fig 344 W U neg 50-689)

In the microscopic examination of carcinoma of the stomach it is important to examine sections from the limits of the resection to determine whether or not tumor is present If the tumor is close to the pylorus a segment of duodenum should be submitted for in these tumors the duodenum is invaded in about 50 per cent of cases (Zinninger) In the duodenum tumor may be seen within the

lymphatics and it can be present in almost any layer except the mucosa (Fig 345) Carcinoma close to the esophagus commonly invades it.

If carcinoma of the stomach is exceedingly undifferentiated or if it is of the linitis plastica type, stains for epithelial mucin may be helpful. If this stain is positive it proves carcinoma rather than a sarcoma. Of course highly undifferentiated carcinoma may secrete no mucin



Fig 345 —Gross photograph of an ulcerating carcinoma of the stomach growing in the region of the pylorus where it has invaded the duodenum. The duodenum is at the left.

Clinicopathologic Correlation.—It is unfortunate that carcinoma of the stomach is so often incurable If the tumor does not grow in the cardioesophageal or pyloric areas, there will be no obstruction and the early symptoms may be vague and nonspecific weight loss anemia, and minimal gastrointestinal symptoms In a few instances the first sign of a carcinoma is the presence of lung metastases, a supraclavicular lymph node or liver involvement. The so-called Virchow's node in carcinoma of the stomach is relatively infrequent. Roentgenographic examination of the stomach will demonstrate the lesion in almost 100 per cent of the cases but in about 10 per cent it will be impossible to d[illegible] whether the lesion is benign or malignant Unfortunately tumor sp[illegible] in the stomach, through the wall, and to the[illegible]dant lymph node[illegible]uate and distant zones beyond the possib[illegible]ction (para[illegible]odes and those in the region of the celiac[illegible]spected ext[illegible] to the[illegible] found frequently at oper[illegible]

The pathologic [illegible] specimen [illegible] findings are of great val[illegible] of [illegible]

found at the limit of the excision, the situation is hopeless The microscopic pattern of the tumor is of little or no value in estimating prognosis However the depth of penetration of the carcinoma is of great importance for the deeper the penetration the greater the chance of metastasis Furthermore in groups of cases the smaller the gastric cancer the better the prognosis (Comfort) In a few instances where superficial carcinomas are localized to the mucosa and submucosa the results will be excellent With penetration of the muscular wall the incidence of metastasis increases If no lymph nodes are implicated on thorough pathologic examination over 50 per cent of the patients may be expected to survive for five years. With involvement of lymph nodes the prognosis is poor probably fewer than 10 per cent of the patients survive five years. Steiner has indicated that if the carcinoma pushes through the stomach wall rather than infiltrates it the prognosis is better There are also exceptions in which the pathologic findings show advanced disease but the patient persists in surviving over five years despite them. The reasons for such survival are unknown

An important question has recently been raised as to whether total gastrectomy for a carcinoma of the stomach will yield more cures than so-called radical subtotal gastrectomy (Longmire Lahey) Total gastrectomy is done to prevent local recurrence and to remove a large lymph node bearing area. But if the tumor is located in the pyloric area and a truly radical subtotal gastric resection is done the chances of local recurrence in the remaining stomach is low It seems quite improbable as Walters pointed out that a more adequate resection of the nodes is possible than by subtotal gastric resection. It is true that the operative mortality following total gastrectomy is greatly lowered in experienced hands and is approaching that of subtotal gastrectomy but the morbidity which develops in total gastrectomy is still high Therefore it is highly questionable in our minds whether extending the operation to total gastrectomy in all cases is justified With tumor growing in the region of the cardioesophageal area or high on the lesser curvature indications for total gastrectomy seem better indicated Concepts of what constitutes a radical subtotal gastrectomy differ Certainly in the past the competent surgeon was more conservative than we would be today Therefore the tedious study by McNeer of autopsied patients in which subtotal gastrectomy had been done and local recurrence had developed is of limited value today in discussing the merits of radical subtotal gastrectomy versus total gastrectomy

Lymphosarcoma

Lymphosarcoma of the stomach may be a primary or a secondary manifestation. If it is primary it makes up only a small percentage of all malignant tumors of the stomach about 50 cases have been reported (Taylor) Grossly this lesion has many patterns (Figs 346 and 347) It has its inception in the submucosal lymphoid tissue or within the lamina propria and thus is submucosal in nature. There may be giant convolutions resembling cerebral convolutions and mimicking to some extent a hypertrophic gastritis There may be a tremendous lobulated mass with areas of superficial or deep ulceration In 12 of 34 cases at Barnes Hospital the lesion was polypoid (Snoddy) Because the gross pattern

varies within wide limits one type merges into another This tumor does not usually involve the pylorus We feel that it cannot be distinguished from carcinoma with certainty either grossly or radiographically

Lymphosarcoma may remain restricted to the stomach, but it frequently involves regional nodes to form a voluminous mass. Microscopically it can be made up of either small or large cells, or it can show the giant follicle type lymphoma

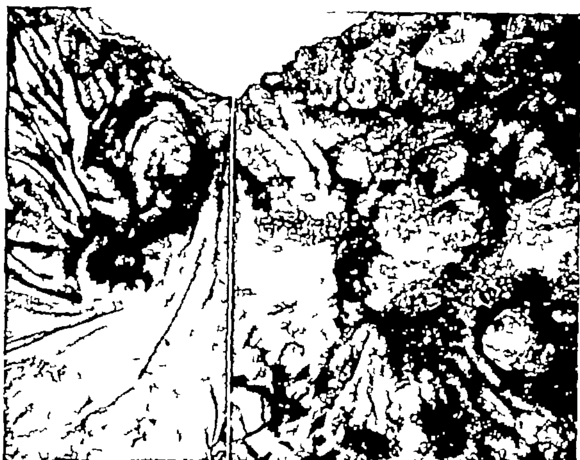


Fig 346 —Gross photograph of a lymphosarcoma which presented as an ulcer (W U neg 50-6055)

Fig 347 —Gross photograph of diffuse involvement of the stomach by lymphosarcoma. (W U neg 50-390)

(Fig 348) Rarely the tumor is limited to the mucosa (Puente Duany) suggesting origin from lamina propria. It is sometimes difficult to distinguish reticulum-cell sarcoma from an undifferentiated small-cell carcinoma. However if there is no transition from normal to abnormal epithelium, if the muscularis mucosae is intact if the cells contain no mucin, and no suggestion of acinar pattern is seen the tumor is probably reticulum-cell sarcoma Response to irradiation may be helpful in differentiating these two neoplasms.

Patients with lymphosarcoma may have a large palpable mass and still be in excellent physical condition. The diagnosis of lymphosarcoma is not usually made clinically or radiographically The history often suggests peptic ulcer at times *perforation can occur* Lymphosarcoma of the stomach is more curable than

carcinoma of the stomach as cure can be effected either by surgery or by appropriate irradiation Operable cases are usually resected often with a diagnosis of carcinoma rather than lymphosarcoma Inoperable cases are sometimes biopsied and if radiosensitive lymphosarcoma is found and given radiotherapy, cure or long term survival may result There are about as many cases of lymphosarcoma cured by surgery as are cured by irradiation, but it is not known which method of treatment is the best



Fig 348—Photomicrograph of a lymphosarcoma of the stomach which has spread through the wall and ulcerated the surface (Low power) (W U neg 50-5217)

It is worth stressing that reactive lymphoid hyperplasia of the stomach may closely simulate lymphoma (Smith) Smith has reported 42 cases. We have had difficulty with this lesion particularly when the lesion has been present fairly deep in the muscle but the presence of lymph follicle formation and distinct intermingling of other cells, such as plasma cells commonly seen in chronic inflammation has been helpful Naturally the regional lymph nodes in such cases would show only hyperplasia. It is probable that this lesion accounts for some of the reported cures of lymphosarcoma of the stomach

Rare Tumors

Primary rare tumors such as carcinoid (Lattes) glomus (Kay) lipoma (Peabody) and plasma cell tumors have been reported. Metastatic carcinoma may occur in the stomach from any widely disseminating neoplasm. Mixed adenocarcinoma and squamous carcinoma have been reported in the pyloric portion of the stomach (Wood)

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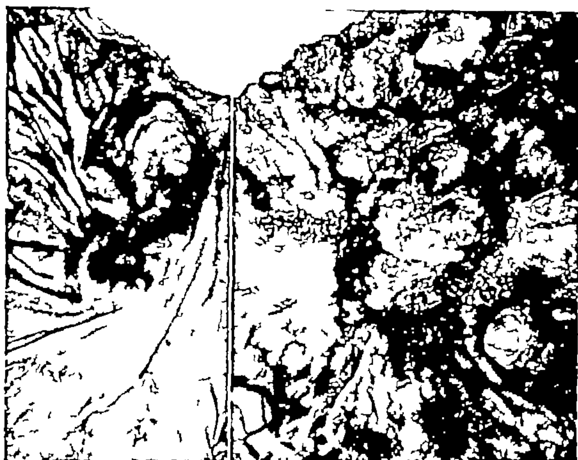


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SMALL INTESTINE

DUODENUM
- Peptic Ulceration
- Adenocarcinoma

JEJUNUM
- Acute Jejunitis
- Jejunal Ulcer

SMALL BOWEL
- Regional Ileitis (Cicatrizing Enteritis, Crohn s Disease)
- Congenital Defects
  - Heterotopic Pancreas
  - Duplication
  - Meckel's Diverticulum
- Irradiation Effect
- Intussusception

TUMORS
- Benign Tumors of Epithelial Origin
- Adenocarcinoma
- Smooth Muscle Tumors
- Lipoma
- Lymphosarcoma
- Carcinoid Tumors
- Rare Lesions

DUODENUM

Peptic Ulceration

Peptic ulceration of the duodenum is one of the most common lesions encountered in surgical pathology Partial gastric resection may not encompass the ulcer and only in a few instances is complete excision of the ulcer performed Peptic ulceration probably occurs as a sequel to disturbed gastric function which relates to significant psychologic stresses of life (Wolf)

Grossly this chronic single lesion is usually within 2 cm of the pylorus although it may occur in the second portion of the duodenum (Warmoes) (Fig 349) When the ulcer is in the latter position it may be the source of upper abdominal pain and bleeding yet not be discernible radiographically Peptic ulcer has well defined margins sharply set off from the surrounding mucosa At times a large vessel with an open lumen may be seen at the base of the ulcer Fibrosis of a healed ulcer may produce secondary diverticuli and considerable shortening of the duodenum. Peptic ulcer of the duodenum does not become malignant. Multiple duodenal nodules may be due to focal hyperplasia of Brunner s glands.

Adenocarcinoma

Carcinoma of the duodenum is an extreme rarity although it can arise from the mucosa in the region of the ampulla. This entity has been described under tumors of the periampullary region. Carcinoma arising elsewhere in the duodenum is extremely rare we have seen one carcinoma in the second portion of the du odenum arising from heterotopic pancreas



Fig 349 —Chronic penetrating ulcer of the first portion of the duodenum. In planning to remove a large part of acid and pepsin-secreting tissue the greatest concentration of secretory cells is in the body of the stomach near the antrum, and this concentration of cells is highest on the greater curvature (Cox) (W U neg 49 2144)

JEJUNUM

Acute Jejunitis

This rare entity usually occurs with equal frequency in both men and women over the age of 55 The pathogenesis is obscure but Brynjulfsen has suggested that a virulent organism penetrates the intestinal wall through a mucosal flaw Grossly the involved loop of bowel is sharply demarcated and the inflammation present is mainly in the mucosa There may be pus on the serosal surface (Fig 350) The bowel itself is somewhat edematous and frequently slightly distended. It may in volve the jejunum of the duodenum. Microscopically there is frequently a wide-

spread lymphangitis and lymphadenitis, and the lymph nodes are often slightly enlarged The mesentery has a somewhat glassy appearance Abscesses between the walls of the mesentery have been observed Primary ulceration of the jejunum is rare and of unknown etiology (Berry)

Jejunal Ulcer

Pathogenesis of the Jejunal Ulcer—Marginal ulcer although it may be actually stomal in position is usually situated on the wall of the jejunum away from the gastroenterostomy opening This type of peptic ulcer is a complication of gastroenterostomy and of gastric resection (Billroth II) for duodenal ulcer It is rarely seen after gastric resections for benign gastric ulcer or cancer of the stomach It eventually occurs in a high proportion of patients who have gastroenterostomy alone for duodenal ulcer Jejunal ulceration is more likely to occur after gastric resection for duodenal ulcer if the extent of the resection has been inadequate, if the entire antrum is not removed and if the afferent jejunal loop is of excessive length

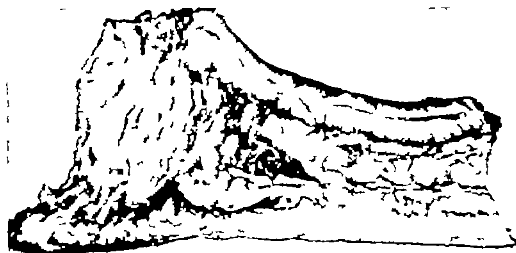


Fig 350—Gross specimen of phlegmonous jejunitis. Note fibrin on the surface of the bowel. (W U neg 50-5538)

SMALL BOWEL

Regional Ileitis (Cicatrizing Enteritis, Crohn's Disease)

Regional ileitis occurs with equal frequency in males and females in their twenties or thirties Often there is a background of psychologic disturbances Grossly the ileum is commonly involved although all portions of the small bowel can be involved. In Dixon's 44 cases the ileum was involved in 43 The duodenum is practically never affected except with extensive disease we have seen only one case. Regional ileitis can also spread to involve the large bowel. Usually there are multiple areas, and there may be poor or sharp delineation at the margins Early in the disease the involved small bowel has a soggy feeling and reddish purple surface. In advanced involvement of the bowel the impression on palpation has been compared to "an eel in rigor mortis (Dalziel) Ulceration may be very

prominent, and the lumen may be narrowed to 0.5 cm. (Fig 351) The bowel proximal to the obstruction may be dilated and hypertrophied In advance stages of the process there may be fistulas between loops of small bowel between small

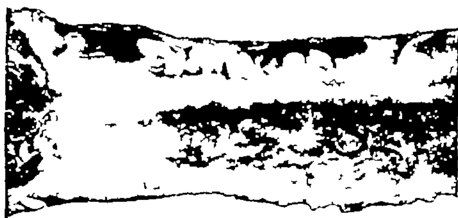




Fig 351.—Gross specimen of cicatrizing enteritis with superficial ulceration present with submucosal and subserosal fibrosis. The muscle can be clearly seen. (W U neg 49-803)

Fig 352.—Surgically resected gross specimen of cicatrizing enteritis. Note irregular narrowing of the lumen with shortening of the mesentery (W U neg 50-4370)

and large bowel, between bowel and abdominal wall, and between bowel and bladder Fibrosed mesentery produces irregularities in the contour of the bowel, which may be somewhat corrugated. Later on there may be subserosal fibrosis, shortening of the mesentery and enlargement of the regional lymph nodes (Fig 352)

Microscopically the earliest changes are those of submucosal edema. With prominent lymphadenoid hyperplasia there may be superficial ulceration (Blackburn) (Fig 353) In the submucosa there is an inflammatory infiltrate made up mainly of plasma cells, lymphocytes and eosinophils The submucosal and myenteric nerve plexuses are often prominent probably due to edema of the bowel rather than to any intrinsic changes in the nerve plexuses. Blackburn emphasizes



Fig. 353 —Photomicrograph of cicatrizing enteritis. There are ulceration submucosal fibrosis lymphadenoid nodules dilatation of lymphatics and subserosal fibrosis. (Low power) (W U neg 50-5222)

the changes in the lymphoid nodules and indicates that with the passage of time the pale endothelial cells develop in the germinal centers and are gradually replaced by giant cells which he calls "giant cell systems" (Fig 354) These areas never become necrotic or caseous. The same changes may occur in the prominently enlarged regional lymph nodes. These nodular granulomatous zones are quite specific for this entity The early submucosal thickening is due to lymphedema. Often the muscularis mucosae is hypertrophied (Rappaport) Foreign body type giant cells may be present (Fig 355) With still further passage of time

intramural abscesses appear Inflammatory changes occur with fibrosis of the muscle and subserosa. Blackburn states

> The primary lesion in regional ileitis is a specific hyperplasia of the lymphadenoid tissue of the submucosa extending to the regional lymph nodes. It gives rise to lymphatic obstruction and edema, which in turn causes ulceration and nonspecific infection.

This attractive hypothesis he further supports by quoting the experimental work of Reichert who injected irritating substances into the mesenteric lymphatics of dogs producing lesions resembling regional ileitis. No one as yet has been able to repeat these experiments.

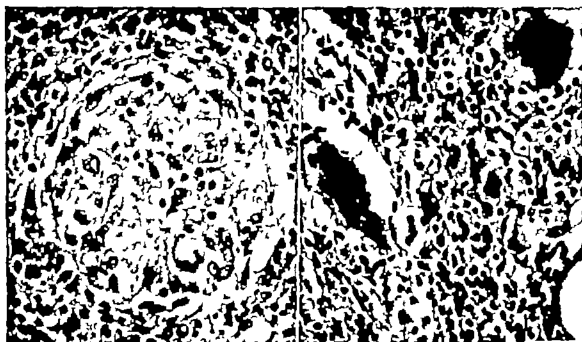


Fig 354 —Photomicrograph of reticulum cell hyperplasia in a lymph node as described by Blackburn. (×400) (W U neg 51-6011)

Fig 355 —Photomicrograph of granulomatous area with giant cells in small interstitial lesions of the regional ileitis. (×400) (W U neg 51-6010)

Cicatrizing enteritis has an undulating but progressive course. Infrequently there may be spontaneous regression.

The treatment of choice of patients with regional ileitis is psychiatric and dietary in the absence of complications of disease. Surgical therapy is indicated with the development of partial or complete intestinal obstruction internal or external fistulas perforation with abscess hemorrhage, and intractability despite medical management. Specific operative procedures to be utilized in these patients should be individualized. However resection o lved small bowel seems preferable to side trackin rocedures when the of the patient is not critical. The early acu regional ileitis v monly encountered at laparotomy for a hould not be re these instances, appendectomy may be per ut fear of subs a formatio the cecum is not involved by ry process.

Rare solitary ulcers of the ileum have an unknown pathogenesis and signs of their presence may occur following perforation (Brown)

Congenital Defects

Heterotopic Pancreas.—Heterotopic pancreas may undergo any pathologic changes seen in the normal pancreas It consists mainly of ducts and lobular tissue usually without islet tissue. Blockage of the duct can occur where it empties into the intestinal tract, and this block can cause infection and fat necrosis Rare cases of islet cell tumors within this heterotopic pancreas have been reported (de Castro Barbosa) and we have seen carcinoma arising within it.

Duplication—Duplication of the gastrointestinal tract occurs most commonly in the ileum. Those of the colon and stomach also are not rare. The duplication may be accompanied by inflammatory changes and those of the small intestine may or may not extend to and communicate with the lumen of the large bowel (Ladd) Nearly all of them are incomplete there is a common muscular wall between the gastrointestinal tract and the duplication. This prevents the surgeon from separating the duplication from the intact gastrointestinal tract In other words duplication must be treated either by resection of the area of gut including its duplication or by removal of its walls which are not a part of the wall of the intact gut.

Meckel's Diverticulum.—Meckel's diverticulum is found in 2 per cent of all persons but is more common in males (63 per cent) Early in fetal life the intestine communicates with the yolk sac for nourishment. By the fourth week the opening has gradually narrowed to form a tubular structure known as the vitelline duct At the 7 mm. stage the midgut normally closes off completely by atrophy of the vitelline duct to form a fibrous cord. This fibrous cord between the umbilicus and bowel is subsequently absorbed. Failure of all or part of the vitelline duct to become obliterated accounts for the various forms of this lesion. The remaining fibrous cord extends from diverticulum to umbilicus to adjacent bowel, or to mesentery The vitelline duct may remain patent throughout, causing entero-umbilical fistula. Persistence of the proximal portion of the duct only results in formation of Meckel's diverticulum.

Aberrant pancreatic tissue may be present in the wall of Meckel's diverticulum. Gastric, duodenal, or colonic mucosa may occasionally form part or all of the mucosal lining of the diverticulum (Figs. 356 and 357) The usual location is 80 cm. proximal to the ileocecal valve with origin from the antimesenteric border The average length is 1 to 8 cm. About 30 per cent have other congenital abnormalities. The diverticulum may perforate ulcerate, or intussuscept. Intestinal obstruction can occur from unabsorbed bands. Peptic ulceration of the ileum adjacent to Meckel's diverticulum is a common cause of massive hemorrhage in children

Irradiation Effect

Roentgenotherapy of malignant tumors within the peritoneal cavity may cause damage to the intestinal tract, the amount of damage depending on many factors

It occurs most frequently in patients treated for carcinoma of the cervix Grossly the surface of the small bowel often shows increased fibrosis. The wall may be partially replaced by fibrous tissue, and the submucosa greatly thickened. In these advanced cases mucosal ulceration is often observed at the time of surgical resection. Microscopically early irradiation effect may be demonstrated by an increased production of mucus (Warren) and by nuclear changes in the lining epithelium. Later submucosal edema occurs which may be completely reversible. If the damage is severe, there is fibrosis of muscular wall and ulceration. Infection often complicates the picture Vascular changes are rather minimal in extent, or if present to any degree are secondary to the infection which so often accompanies severe irradiation changes

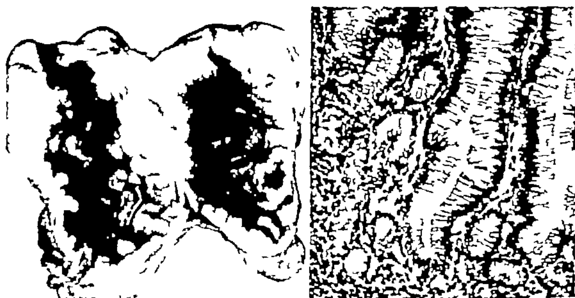


Fig 356 —Gross specimen of perforated Meckel s diverticulum. The area of perforation can be seen on the surface farthest from the caption. (W U neg 48-4286.)

Fig 357 —Photomicrograph of section from the perforated Meckel s diverticulum to show normal gastric glands which contain parietal cells. (×85) (W U neg 48-4308)

Intussusception

Intussusception occurs for the most part in the first two years of life over one half the cases occur in the first year It is rare after the age of 5 This process is two or three times more common in the male During the first year of life, the amount of lymphoid tissue in the ileocecal valve and the degree of projection of the valve into the cecum is at its maximum Both of these decrease during the second year Similar relation exists between the amount of lymphoid tissue in the last few inches of ileum and the incidence of ileocolic intussusceptions Ileocecal valve intussusceptions are the commonest and lymphoid tissue is the most prominent there. Furthermore the lumen of the last portion of ileum is relatively small in the first year of life The reason this cause of intussusception has not been apparent is first that intussusceptions are frequently reduced and, second if an intussusception is resected, it is advanced and inflammation obscures underlying etiology This

entire hypothesis has been supported by Perrin and more recently by Saraso We have seen an instance in which such focal lymphoid hyperplasia was erron ously considered to be a neoplasm and was resected (Fig 358) In the older ag group this condition is frequently accompanied by pedunculated tumor such as lipoma often with a long pedicle arising within the submucosa In children intu susception occurs predominantly in the ileocecal region A length of intestin (the intussuscipiens) literally swallows by telescoping part of the bowel just pro imal to it. This swallowed portion (the intussusceptum) is drawn down with the intussuscipiens until it can go no further because of traction of the mesenter Traction and compression shut off circulation to the intussusceptum which ma become necrotic and be sloughed off The upper ends of the intussuscipiens ar the intussusceptum become firmly united and end to-end anastomosis takes plac



Fig 358 —Gross photograph of extreme lymphoid hyperplasia of the ileum with intussusce tion in a child aged 4 (W U neg 53 7041)

However such an occurrence is extremely rare. The intussusceptive mass of in testine has a curved sausagelike form with concavity toward the mesenteric a tachment at the spinal column. If surgery is done early manual reduction of th intussusception is possible. In the advanced cases surgical resection is necessar Mortality is directly related to the time which elapses between onset and operatio In children there is a rapid rise in mortality after the second day *In early uncom plicated cases a barium enema may be used to reduce the intussusceptio* (Ravitch)

Tumors

Benign Tumors of Epithelial Origin —Benign tumors of epithelial origin of th small bowel are infrequent We have seen rare polypoid tumors sometimes hav ing the appearance of the so-called villous papilloma, and others were like polyp

seen in the large bowel. These polyps may be single or multiple, they may be pedunculated or sessile, and like polyps in the large bowel may undergo cancerous change (Fig 359) Adenomatous polyps of the small intestine are commonly present among persons having familial melanin pigmentation of the lips and oral mucosa (River)

Adenocarcinoma.—Adenocarcinomas of the small bowel are similar to those of the large bowel They usually present a fairly typical gross pattern often forming a napkin ring defect with prominent narrowing of the small bowel due to complete encirclement and invasion by the tumor (Fig 360) The bowel proximal to the tumor is frequently widely dilated Microscopically these tumors are usually moderately well-differentiated adenocarcinomas which have extended through all layers of the bowel to involve the regional lymph nodes. The prognosis is consequently extremely poor

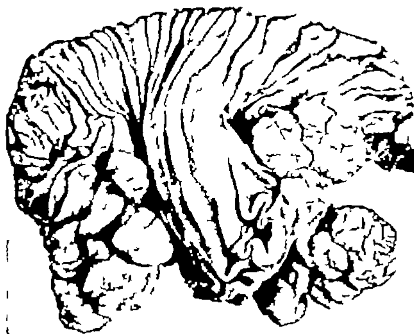


Fig. 359 —Gross specimen of resected small bowel to demonstrate multiple benign adenomatous polyps. (W U neg 49-6157)

Smooth Muscle Tumors.—Smooth muscle tumors of the small bowel may occur in any portion may grow in any of the muscular layers including the muscularis mucosae and may grow toward or away from the lumen. They produce signs and symptoms depending upon their gross pattern. Grossly they are fairly well delineated. Those that grow away from the lumen cause few symptoms, while those that grow toward the lumen cause prominent symptoms. Smooth muscle tumors present intraluminally may be the source of occult or prominent bleeding They may have a central niche similar to those within the stomach if they grow toward the mesentery, they may form a fairly large bulky mass. They may be suspected of being malignant if they are cellular and soft. There are seldom any regional metastases, for these tumors tend to invade the blood stream and metastasize distantly The microscopic differentiation between the benign and malignant

smooth muscle tumor may be extremely difficult. *Generally speaking tumors with* many mitotic figures are malignant On the other hand, well-differentiated neoplasms with practically no mitotic figures may later metastasize and prove the pathologist wrong Fortunately, such an occurrence is rare (Figs. 361 362, 363)



Fig 360—Gross specimen of classical constricting adenocarcinoma of the small bowel with large metastasis. This case although hopeless was found at the time of exploratory laparotomy for gall bladder disease. (W U neg 50-3798)

Lipoma.—Lipomas of the small bowel characteristically grow in the submucosa and for that reason may cause signs and symptoms of intussusception. Grossly they resemble lipomas seen in other locations, bulge upward into the mucosal surface and in time may ulcerate. They do not undergo malignant change.

Lymphosarcoma.—Lymphosarcoma may involve the bowel primarily or as part of a widely disseminated process. It is probably the most common primary malignant lymphoma to involve the small bowel. It commonly occurs in young children frequently in males. This tumor grossly produces a rather characteristic garden hose effect in which the involvement of the bowel is rather sharply de

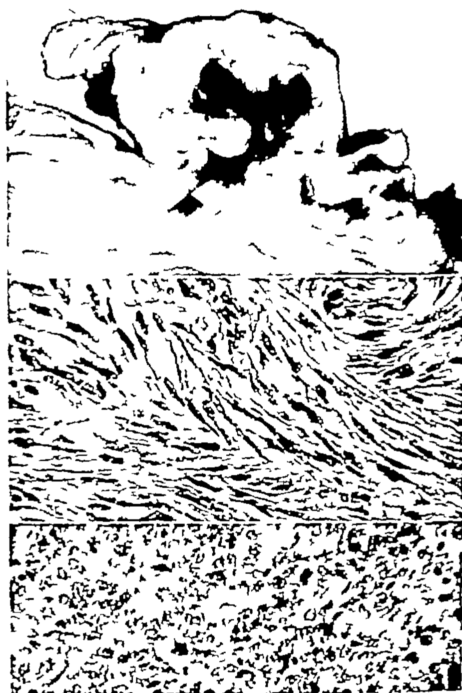


Fig. 361.—Gross photograph of a smooth muscle tumor of the jejunum of long clinical duration which was grossly and microscopically thought to be benign. Note classical central excavation. (W U neg 49-6469.)

Fig 362.—Photomicrograph of the tumor illustrated in Fig 361 showing well-differentiated smooth muscle cells. Mitotic figures were rare. (×510.) (W U neg 52 2875.)

Fig 363.—Two years later the tumor shown in Figs. 361 and 362 locally recurred and metastasized to the liver. The tumor was highly undifferentiated in the liver but there were other areas which showed the smooth muscle origin. (×500.) (W U neg 52-2876.)



Fig 364—Gross surgical specimen of a large lymphosarcoma of the small bowel which replaced all layers and showed prominent dilatation. (W U neg 49 2033)



Fig 365—Gross specimen of Hodgkin's disease of the small bowel This process has destroyed the entire wall of the bowel and there were multiple areas of ulceration present.

lineated and forms a bulky tumor mass frequently with involvement of the regional lymph nodes Cross section of the tumor reveals the wall of the bowel to be completely replaced by homogeneous fish flesh cellular tissue. The mucosal surface has often been completely destroyed. The extent of involvement together with the gross appearance should make the diagnosis (Fig 364) Microscopically all types of lymphosarcoma are seen, from the small lymphocytic type to the large cell type, often designated as reticulum cell sarcoma. Patients with lymphosarcoma of the small bowel, particularly children, do poorly and only rare cases are ever cured either by surgery or irradiation. Rarely *Hodgkin s disease* can involve the small bowel (Fig 365)



Fig 366 —Gross specimen of a carcinoid tumor of the small bowel. Note the buckling of the bowel with hypertrophy of the muscle. The bulk of the tumor lies above the muscle (W U neg 49-4120.) (Specimen contributed by Dr W Hall Chambersburg Pa.)

Carcinoid Tumors.—Carcinoid tumors occur mainly in the ileum but can occur rarely in other portions of the small bowel, even the duodenum. They are frequently multiple. The mucosa is often intact over them. At times they grow large enough to involve the entire wall of the bowel and with the accompanying fibrosis may cause buckling of the bowel wall (Fig 366) On section they commonly have a bright yellow color because of their increased fat content. There may be regional lymph node involvement and metastases within the liver (serotonin syndrome) *Microscopically carcinoid tumors may have a somewhat variable pattern*, but the usual pattern is that of monotonous-appearing cells with small nuclei, inconspicuous cytoplasm, and fine nucleoli. Mitotic figures are rare. In our experience epithelial mucin is not produced by the tumor (Figs. 367 and 368) These tumors are malignant neoplasms which have a slow growth rate, but eventually metastasize



Fig 367.—Photomicrograph showing the characteristic pattern of the carcinoid tumor growing just beneath the thinned overlying epithelium. (Low power) (W U neg 49 1622)

Fig 368.—Photomicrograph moderate enlargement of the carcinoid tumor. Individual tumor cells are uniform with small nuclei and fine nucleoli. Mitotic figures are rare. (×400) (W U neg 49 1621)



Fig 369—Gross photograph of a cavernous hemangioma of the small bowel which had ulcerated the mucosa. The patient had had repeated gastrointestinal hemorrhages from an obscure source which could not be located radiographically It was found at time of exploratory laparotomy (W U neg 52 1844)



Fig 370—Gross specimen of metastatic carcinoma involving the small bowel. The tumor metastasis appeared first in the submucosa and finally ulcerated the surface. Note how normal mucosa extends to the edge of the ulceration. This finding helps to differentiate it from primary carcinoma (W U neg. 50-5539)

and cause the death of the patient It is worth while to resect these tumors even in the presence of metastases in the liver because life may be prolonged several years by resection Thorson has described a distinctive syndrome associated with carcinoid tumors with metastases to the liver In this syndrome there is cyanosis of the skin valvular disease of the right heart and frequent watery stools This syndrome is caused by a substance elaborated by the tumor designated as serotonin, which has vasoconstrictive properties This substance can be identified in the urine through a specific color test (Sjoerdsma) We have seen two instances of this syndrome in which the diagnosis was made clinically, substantiated by the specific color test and then proved pathologically

Rare Lesions.—Benign vascular tumors of the small bowel may be single or multiple and may be associated with hemangiomas in other organs (Hansen Shepherd) They can give rise to bleeding of obscure nature and rarely can perforate into the peritoneum or retroperitoneum. Grossly the lesion is not well delimited and on compression is often soft and the center of the lesion blanches. Microscopically a cavernous hemangioma is usually present (Fig 369) Rarely *metastatic carcinoma* involves the small bowel and may cause symptoms of obstruction necessitating palliative resection (Fig 370) Small bowel obstruction can be caused by endometriosis (Kinder)

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Fig 369 —Gross photograph of a cavernous
ulcerated the mucosa. The patient had had rep
obscure source which could not be located rad
ploratory laparotomy (W U neg 52 1844)



Fig 370 —Gross specimen
tumor metastasis appeared first in
normal mucosa extends to the ec
from primary carcinoma. (W U

APPENDIX

APPENDICITIS

The appendix is a vestigial organ serving no useful purpose in man. It frequently is the site of inflammatory complications requiring its removal. Appendicitis is a disease occurring most frequently in young males but can occur in either sex at any age. It is a disease of the Western world and is common in Great Britain and America. In Asia and Africa, it is reported infrequently. This difference may be based on a dietary variance. Appendicitis occurs where the diet is reduced in bulk with diminished cellulose and high protein intake. The mucosa of the normal appendix has a light yellowish tint and its surface is smooth and glistening. Mucosal hemorrhages and hyperemia of surface vessels are usually related to operative trauma whereas a fibrinous or purulent coating indicates a pathologic process. In children from age 10 to young adults, *diffuse lymphoid hyperplasia* may produce enough obstruction in the lumen to cause appendicitis (Nathans Gray). In this country about 3 per cent of appendices removed show *Oxyuris vermicularis* infestation (Ashburn). These parasites are most commonly found in the appendices of children between the ages of 7 and 11 years. This infestation is not a causal agent of appendicitis but occurs with about the same frequency in normal appendices. A true or false diverticulum (usually false) may be the site of an acute inflammation.

Wilkie has demonstrated in the rabbit that if fecal material is milked into the lumen of the appendix and then the appendix is ligated the rabbit dies within twenty four hours from a perforated gangrenous appendix. If the rabbit's appendix is free from infection and is ligated mucocele alone results. Wangensteen has demonstrated in human beings that there is active secretion of fluid by the appendiceal mucosa the highest secretory pressure was 126 cm. of water after fourteen hours of obstruction. He found that under certain circumstances the balance between secretion and absorption was narrow with fibrosis there was diminished secretory capacity. This finding may be responsible at least in part for the diminished incidence of appendicitis in the older age group. A normal

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monly in the right iliac fossa lateral to the cecum (Figs 373 and 374) Variations in location are related to the site of the appendix Large abscesses may perforate into the cecum or rectum or even extend to the skin surface We have seen a single instance of acute necrotizing arteritis in the vessels of the appendix (Fig 375) probably on an allergic basis



Figs. 371 and 372 —Gross specimen of the appendix from a 5-year-old child who had symptoms of appendicitis. No real evidence of acute inflammation is present. Complete obliteration of the lumen by lymphoid tissue is seen. Photomicrograph confirms gross appearance. (Low power) (Fig 371 W U neg 49-5584 Fig 372 W U neg 49 3706)

In the rare lesion of the appendix which occurs in the prodromal stage of measles the patient develops appendicitis and the microscopic examination shows proliferation of the endothelial cells with the presence of many multinucleated giant cells (Fig 376) Similar changes have been reported in the tonsil If the

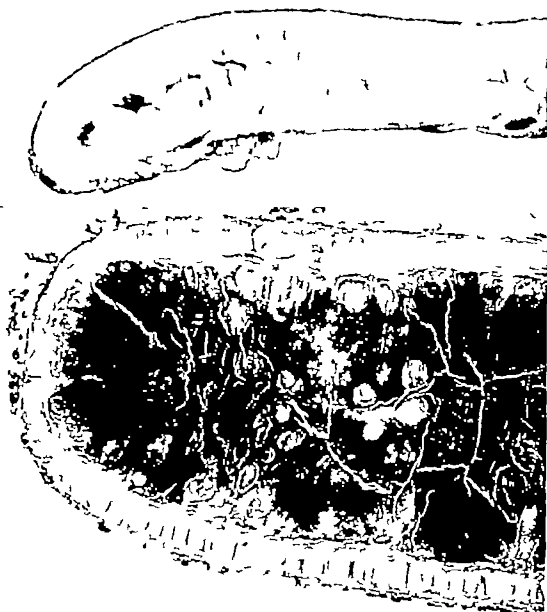
appendix is, therefore more vulnerable to distention by partial obstruction than the fibrosed appendix. Acute inflammation particularly in the normal appendix, occurs when there is *secretion under pressure behind an obstruction* sufficient to impair the resistance of the normal wall to infection. This obstruction is usually a *fecolith* but it may be a foreign body true calculi (Clark) a gallstone, a carcinoma of the cecum or a primary tumor of the appendix. With infection and dilatation beyond the area of the block, an inflammatory process may progress to the point of complete necrosis of the appendix with perforation and peritonitis. The obstructive type is more likely to lead to perforation. Nonobstructive appendicitis can be related to a generalized infection, particularly in the respiratory tract. It is possible that nonobstructive appendicitis in the aged is due to diminished lymphatic tissue, a thin fibrous appendix and vascular changes (Taylor Boyce Simpson) In New Orleans the age group over 39 accounted for the smallest number of cases and the greatest number of deaths

Acute Appendicitis

In an acute appendicitis there is close correlation between the gross and microscopic findings Therkelsen reported 154 acute appendices 125 demonstrated gross evidence of change 25 showed doubtful evidence of change, and 4 appeared normal. In the apparently normal appendices focal changes localized to a small area of mucosa may occur In acute appendicitis the external appearance shows fibrin and variable amounts of pus and the mucosa may be necrotic and ulcerated. Frequently a fecolith is impacted in the lumen. The process may become localized, however with the formation of an appendiceal abscess. In the presence of an acute inflammatory process secondarily infected thrombi rarely form and spread to the ileocolic and upper mesenteric veins.

Microscopically the diagnosis of appendicitis is relatively simple. The sections are usually taken throughout the length of the appendix, but at times appropriate sections must be made in the inflamed and dilated appendix In the *lymphoid hyperplasias* of children and young adults there may be such pronounced hyperplastic lymphoid tissue that it balloons into the lumen causing complete obstruction (Figs. 371 and 372) In the presence of *Oxyuris vermicularis* minimal or no inflammatory changes are present. In the *acute inflammatory processes* minimal inflammation to necrosis and complete destruction of the wall of the appendix may occur In the early lesion neutrophils appear at the base of the crypt adjacent to a small defect in the epithelium. After this inflammatory process reaches the submucosa it spreads quickly to the remaining appendix. Lymphangitis is usually widespread. In advanced stages the mucosa may be destroyed and the wall necrotic, and thrombosed vessels may be present. These thrombosed vessels are secondary to the acute process and occurred in 26 out of the 100 cases reviewed by Remington Pylephlebitis may originate in a thrombosed vessel of the diseased appendix and spread to the ileocolic and upper mesenteric veins finally to involve the portal veins. The appendices of these persons will show pathologic alterations, depending on the time interval between the acute attack and the operation. With perforation, abscess formation can occur The abscess is com

monly in the right iliac fossa lateral to the cecum (Figs 373 and 374) Variations in location are related to the site of the appendix Large abscesses may perforate into the cecum or rectum or even extend to the skin surface. We have seen a single instance of acute necrotizing arteritis in the vessels of the appendix (Fig 375), probably on an allergic basis



Figs. 371 and 372 —Gross specimen of the appendix from a 5-year-old child who had symptoms of appendicitis No real evidence of acute inflammation is present. Complete obliteration of the lumen by lymphoid tissue is seen. Photomicrograph confirms gross appearance. (Low power) (Fig 371 W U neg 49-3584 Fig 372 W U neg 49 3706)

In the rare lesion of the appendix which occurs in the prodromal stage of measles the patient develops appendicitis and the microscopic examination shows proliferation of the endothelial cells with the presence of many multinucleated giant cells (Fig 376) Similar changes have been reported in the tonsil. If the



Fig 373 —Gross photograph of a periappendiceal abscess. This abscess was palpable clinically there was also a defect seen radiographically in the cecum. (W U neg. 52 1976)



Fig 374 —Radiograph showing detailed view of defect in the ileocecal area. This lesion was misinterpreted as carcinoma and was radically removed. (W U neg 57 1352.)

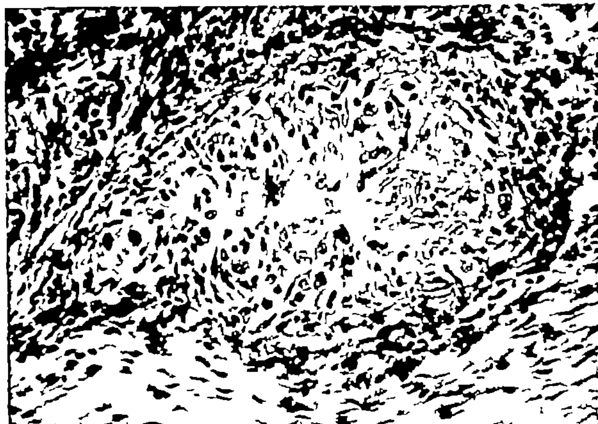


Fig 375 —Photomicrograph of necrotizing arteritis of the appendix in a child with possible rheumatic fever (×325) (W U neg 57 3371A.)

Fig 376 —Photomicrograph demonstrating the typical giant cells appearing in the appendix of a child in the prodromal stage of measles. (×350) (W U neg 57-4625) (Slide contributed by Dr J L. Bonenfant, Quebec, Canada)

pathologist is astute enough to recognize these changes he can tell the patient's physician that the child is about to break out into the characteristic rash of measles (Galloway Bonenfant)

Clinicopathologic Correlation—Acute appendicitis continues to be the most common acute surgical illness treated in general hospitals. In 1886 Fitz through his thorough studies demonstrated that the appendix was the origin of mysterious right iliac fossa inflammation. Three years later McBurney emphasized the principles of accurate early diagnosis and prompt surgical intervention. By 1900 the mortality rate had fallen to 35 per cent. During the next three decades, it was further reduced to 5 per cent as a result of dissemination of knowledge to the



Fig 377—Obstructive appendicitis distal to an obstructing fecalith. (W U neg 49-5325)

public and physician concerning the symptoms and signs of acute appendicitis, the need for early surgical intervention, and the dangers of catharsis and morphine for undiagnosed abdominal pain. In the following 25 years a combination of improved surgical technique better pre and postoperative care advances in anesthesiology and the development of effective antibacterial agents led to further declines in mortality to a fraction of 1 per cent The latter reduction in risk was accomplished mainly in three classes of patients those with perforation and peritonitis, the very young and the very old.

Almond reviewed all the appendices removed in adults in 1954 and all the appendices removed in children in 1954 and 1955 at Barnes Hospital and the St. Louis Children's Hospital, respectively and found that in adults the accuracy of diagnosis was 67 per cent and in children 90 per cent. In spite of the fact that in

31 per cent of the adults and in 36 per cent of the children perforation had occurred there were no deaths (Table 16). It is granted that obstruction is the usual cause of appendicitis and in this series of cases reviewed we could find objective evidence of such an obstruction in 15 per cent of instances (Table 17), a figure much lower than that quoted in the literature. It appears certain that our 45 per cent is an underestimation of the facts. We have looked carefully for local evidence of vascular etiology in the aged, but we have yet to see a single instance that we could prove pathologically.

TABLE 16 APPENDECTOMY FOR ACUTE APPENDICITIS

	ADULTS	CHILDREN	TOTAL
All cases	121	99	220
Acute appendicitis	80 (66.6%)	89 (90.0%)	169
Perforated	25 (31.2%)	32 (35.9%)	57 (33.7%)
Peritonitis	14 (17.5%)	21 (23.6%)	35 (20.7%)
Abscess	11 (13.7%)	11 (12.3%)	22 (13.0%)

TABLE 17 MECHANISMS OF OBSTRUCTION

TYPE	CHILDREN	ADULTS	TOTAL
Fecalith	23	23	46
Lymphoid hyperplasia	6	3	9
Dilatation (cause unknown)	8	11	19
			74

Chronic Appendicitis

There is no doubt that if the clinical signs and symptoms suggest the probability of appendicitis the appendix should be removed. Chronic appendicitis as a primary entity has been greatly disputed. There is no doubt that patients may develop classical signs of acute appendicitis which subsides.

With obstructive appendicitis there is often acute periumbilical colicky pain and reflex vomiting caused by increased intraluminal pressure (Figs. 377, 378, 379). Fever and leukocytosis develop with the onset of peritoneal inflammatory signs in the right lower quadrant. With inflammatory invasion of the muscle, perforation may finally occur rarely with temporary relief of pain. But signs of generalized peritonitis soon appear. Acute appendicitis in children (Packard) and in aged persons (Simpson) may be mishandled because of failure to consider the diagnosis and because the findings are often atypical. Appendicitis can rarely be simulated by infarction of the greater omentum (Aliccc). The extent of these alterations is in turn dependent upon the severity of the previous infection. In some instances where gangrene has occurred only a stump of the appendix remains. In other instances where an inflammatory process has destroyed the muscle fibrous replacement is present. Of course if the process was superficial and confined to the mucosa and submucosa no changes will be found.

The symptoms and signs of chronic appendicitis are as vague and shadowy as the pathology. Primary chronic appendicitis as a pathologic or clinical entity is unlikely. This does not preclude the existence of appendiceal colic without acute inflammation. In the natural development of the appendix fibrosis begin

ning at the tip takes place with aging Such fibrosis does not cause symptoms. Unfortunately in some laboratories the pathologist is a willing accomplice to the surgeon who is liberal in his clinical diagnosis of chronic appendicitis. These pathologists never call an appendix normal Rough handling and clamping of the

Fig 378 —Acute appendicitis with obstruction, perforation and periappendiceal inflammation (W U neg 49 4993)

Fig. 379 —Large inflammatory mass which shows destruction of the wall and fecalith in place. (W U neg 49-4993)

appendix may produce hemorrhage, and with age there is an increase of fibrous tissue with diminished lymphoid tissue lly there may be a collection of lymphocytes in the muscular wall of dix, and a rare plasma cell or eosinophil may be seen in the mucosa. e vague preoperative symptoms disappear is not ily evidence th oms wer way related

to the appendix As Hertzler stated, "The anatomic structure of appendices commonly removed under the diagnosis of chronic appendicitis shows no variation from the appendices of individuals suffering from no abdominal complaint whatsoever The diagnosis "chronic remunerative appendicitis probably is more apt

TUMORS

Mucocele and Pseudomucinous Cystadenocarcinoma (Malignant Mucocele)

In the rabbit with an obstructed appendiceal lumen the epithelium becomes flattened with diminished lymphoid tissue If the block continues, there is production of mucin and dilatation of the lumen When this material in the rabbit is transplanted to the peritoneum it acts as foreign material and in time regresses (Cheng)



Fig 380 —Gross photograph of classic example of mucocele of the appendix still confined within the lumen but showing extreme distention and thinning of the wall This was an incidental finding in an adult female who had had a cholecystectomy (W U neg 53 2882.)

If these changes occur in the human being a globular enlarged appendix results (Fig 380) This appendix contains large amounts of glairy mucus (Figs 380 and 381) The wall of the appendix becomes thin and rupture can occur retroperitoneally or on the free peritoneal surface. In the retroperitoneal area it may form a walled-off mass with areas of calcification. On the peritoneal surface it acts as a foreign body Removal of the appendix is curative. This mucocele should be distinguished from pseudomucinous cystadenocarcinomas of the appendix which are primary malignant rare tumors of the appendix (Woodruff) It is impossible to state with certainty whether a simple mucocele becomes a malignant pseudomucinous adenocarcinoma or whether these two processes are completely independent. Hilsabeck reported 229 cases of benign and malignant mucocele 29 were designated as malignant If perforation occurs with escape of neoplastic cells to the peritoneal surface, they may grow there and appear similar to metastatic pseudomucinous cystadenocarcinoma arising from the ovary This process forms gelatinous nodules and in time may cause the death of the patient through infection or intestinal obstruction by invasion of the surrounding struc

Fig 381 —Photomicrograph of mucocele of appendix. The epithelium is of the colonic type and the wall is thin. (×150) (W U neg 51-6017)



Fig 382 — Gross photograph of a carcinoid tumor of the appendix which blocked the lumen and caused an acute appendicitis. (W U neg 52-4366.)

tures such as the bladder abdominal wall and intestine We have not seen involvement above the diaphragm or metastases to lymph nodes In three instances perforated malignant material spread into a hernial sac and was diagnosed on the basis of examination Pseudomucinous cystadenocarcinomas of the appendix may be associated with similar independent lesions of the ovary (Ries) Radiotherapy may temporarily slow the growth of a metastatic tumor Surgical removal of as much of the tumor as possible may be helpful in prolonging life even for several years. However, the neoplastic tissue closely adheres to the peritoneum and peritonitis is a common postoperative complication

Adenocarcinoma

Few cases of primary adenocarcinoma of the appendix have been reported (Lesnick, Uihlein) Adenocarcinomas of the cecum which have secondarily invaded the appendix have been erroneously reported as primary carcinoma. Carcinoma may be located in any part in the appendix. It may be an incidental finding grossly or even microscopically as preinvasive carcinoma (McCollum) The symptoms resemble acute appendicitis. Treatment depends on the location and stage of the tumor

Carcinoid Tumors

Carcinoid tumors are found in about one out of every 500 routine appendectomies, and in about one half the instances they are incidental findings probably because they commonly develop in the tip of the appendix (Masson) In 50 per cent of instances they completely obstruct the lumen and produce signs and symptoms of acute appendicitis (Fig 382) Grossly they are yellow and replace the wall and are fairly well delineated Microscopically they do not show any difference from those in the small bowel The carcinoids of the appendix are often called benign in contrast to the carcinoids in the ileum but this designation of benign is related to the fact that they are discovered earlier because of obstruction to the lumen of the appendix and therefore are usually cured by appendectomy Proof of their malignancy lies in the 20 patients with metastases reported by Pearson.

Rare Tumors

Primary lymphomas of the appendix have been reported (Galloway) We have seen a primary reticulum cell sarcoma of the appendix in a child cause intussusception and have also observed metastases to the appendix from breast carcinoma (Bolker)

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LARGE BOWEL

DIVERTICULOSIS AND DIVERTICULITIS

Diverticulosis and diverticulitis usually do not appear in patients under 40 years old. About 1 in 8 patients over 45 has diverticulosis but surgical complications occur in only 10 per cent or less of the cases (Mailer). The pathogenesis is probably related to herniation of the mucosa through the muscular defect associated with the nutrient vessels (Neal). Ulceration into these nutrient vessels may cause severe hemorrhage (Noer). About 80 per cent of diverticula occur in the sigmoid, the rest are equally distributed in the remaining portion of the large bowel. Solitary diverticulitis of the cecum may be confused with cancer (Butler). We have seen an instance with perforation and pericolic abscess. The diverticulum has a flasklike shape, fills with feces and cannot empty because there is no muscle in the sac. In time the hernia forces its way through the muscular layer and extends into the appendices epiploicae (Fig. 383). In a fat person it may be difficult to recognize diverticula at the time of operation. Secondary inflammatory changes may occur. Usually the tissues in the immediate area become adherent to the zone of threatened perforation. Acute free perforation is rare. An inflammatory mass usually forms which may be confused with carcinoma (Fig. 384). The spontaneous drainage into bladder or adjacent bowel of an abscess secondary to diverticular perforation results in fistulas.



Fig 383 —Photomicrograph to demonstrate a diverticulum of the large bowel with penetration through the entire muscular wall. (Low power) (W U neg 50-5224)



Fig 384 —Photomicrograph of a diverticulum with perforation and abscess formation. (From Lumb G and Protheroe R. H B A. M A. Arch Path. 62: 185 1956)

Diverticulitis usually involves a much longer segment of the bowel than does carcinoma. It has saw-tooth serrations and a narrowed lumen. However, careful radiographic examination usually shows the mucosa to be intact. Surgical resection is being performed more frequently in patients with diverticulitis in the presence of complications such as perforation, obstruction, hemorrhage, and confusion with cancer (Fig. 385). Other indications are repeated attacks of diverticulitis





Fig. 385.—Radiograph and gross photograph of diverticulosis of the rectosigmoid area. The gross specimen has been fixed and distended to its normal circumference in order that the diverticula can be accurately portrayed. (W U negs 57 990 and 57 4003.)

while on a good medical regime and the development of urinary symptoms. Urinary symptoms may imply impending sigmoid vesicle fistula. Welch reported 114 patients with a resection mortality of 2.6 per cent

ULCERATIVE COLITIS

Ulcerative colitis occurs with equal frequency in both sexes, and it appears most commonly in patients between 20 and 40 but may occur at any age. The etiology is unknown but psychogenic disturbances seem to be important in many cases (Daniels) The gross appearance of the lesion varies with the stage of the disease. The process is thought to begin most frequently in the rectosigmoid area, but it is possible that other areas also are affected early since only the rectal zone



Fig 386.—Roentgenogram showing extensive narrowing of the bowel wall in chronic ulcerative colitis. (W U neg 48-5548)

is easily inspected through the sigmoidoscope. Any portion of the bowel can be affected. The process attacks the ileum in about one third of the cases the appendix is diseased in 20 to 60 per cent of them.

In the early stages of the disease the wall may be slightly contracted due to the thickening of the submucosal and muscular layers. With further extension of the process small and large ulcers appear At times wide areas of mucosa are destroyed and only a few islands of elevated mucosal epithelium persist. In the chronic stage narrow longitudinal gutterlike ulcerations occur between soft, bulbous and edematous mucosa (Figs. 386 and 387) If the process is acute, the mucosal surface of the bowel is wet and glairy from blood and mucus, and

petechial hemorrhages are often seen In the end stages of the process the entire bowel becomes fibrotic and is narrowed and shortened (Fig 388) Infrequently cicatricial stenosis associated with an inflammatory mass may result in an erroneous clinical and radiographic diagnosis of carcinoma We have seen extensive ulcerative colitis in a terminal and quiescent stage There was no ulceration, the mucosa was abnormal, and there was extensive submucosal fat replacement

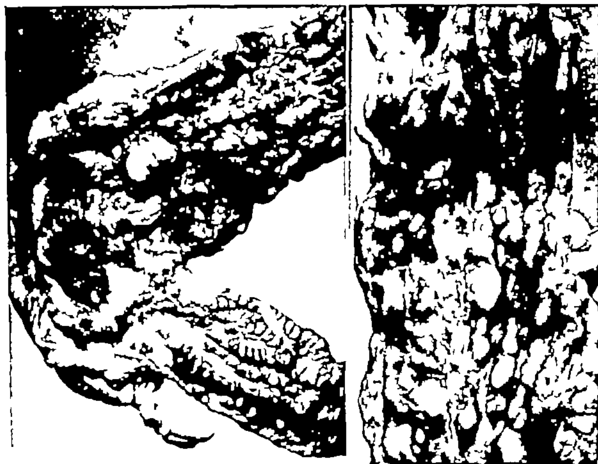


Fig 387 —Gross photograph of ulcerative colitis. Note extension of process to involve the terminal ilium and the pseudopolyps of the large bowel. (W U neg 52 927)

Fig 388.—Detail view of the extensive ulceration with pseudopolyps. (W U neg 52 928.)

The essential lesion of ulcerative colitis is an excessive destruction of undifferentiated cells at the bases of the crypts of Lieberkühn (Lumb) Inflammatory cells penetrate and destroy the villi and form small abscesses at their bases. With progression these abscesses extend along the submucosa. Secondary intestinal changes occurring in ulcerative colitis start at the lumen and progress outward mucosal regeneration hypertrophy of the muscularis mucosae submucosal fibrosis, fatty infiltration, muscular hypertrophy and subserosal fibrosis (Warren) At times *nonspecific granulomas may be present in the bowel wall and in the lymph* nodes. Their etiology is obscure.

When pus escapes in the submucosa, ulceration may develop and mucosal bridges with underlying purulent exudate may form. Beneath the ulcers is granulation tissue containing abundant cells typical of chronic inflammation. The in

The *complications of ulcerative colitis* are perforation with peritonitis and abscess formation venous thrombosis occurring most often in the iliac vein and cancer After ten or more years of ulcerative colitis carcinoma tends to develop at multiple sites in the colon (Fig 392) Carcinoma occurred in 10 out of 226 cases reported by Kiefer Counsell emphasized the atypical gross appearance of the cancer and its rapid spread. Goldgraber emphasized the more even distribution of cancer the multiple foci of origin, the atypical gross appearance, and the fact that cancer occurring in ulcerative colitis tends to be in younger persons. In 63 surgically treated cases of chronic ulcerative colitis, the incidence of carcinoma was 11 1 per cent. In 11 patients who had chronic ulcerative colitis for more than ten years 5 developed carcinoma. In 153 colectomy specimens reported by Dukes (1957), 8 demonstrated cancer The risk of development of cancer in children with chronic ulcerative colitis appears to be a serious one (Holowach) We agree with Warren that cicatrizing enteritis and nonspecific ulcerative colitis are morphologically distinguishable and rarely coexist.



Fig. 392.—Gross photograph of a chronic ulcerative colitis with superimposed carcinoma in region of constriction. The mucosa showed multiple foci of origin. (W U neg 51-4993)

HIRSCHSPRUNG'S DISEASE (IDIOPATHIC MEGACOLON)

The symptoms and signs of Hirschsprung's disease usually begin shortly after birth with gaseous distention and even acute intestinal obstruction In the chronic form the large bowel is hypertrophied and dilated proximal to a narrow segment usually in the sigmoid colon. The pathogenesis of this disorder is related to the lack of parasympathetic ganglion cells in the intramural plexus of the distant colon (Fig 393) These cells are also absent from a segment of the adjoining dilated colon (Fig 394) (Bodian) The distance in the proximal dilated segment in which ganglion cells are absent is variable. Complete absence from the entire proximal

colon has been reported (Zuelzer) In such instances the infant or young chil may present with the clinical picture *of partial or complete intestinal* obstructio When no mechanical obstruction is found at operation and there is no apparer cause for paralytic ileus the cecum should be biopsied and examined *by froze* section If ganglion cells are absent temporary ileostomy may be life savin



Fig 393—*Intramural plexus in narrow segment in a patient with Hirschsprung's disea* showing absence of ganglion cells (×360) (W U neg 51 188)

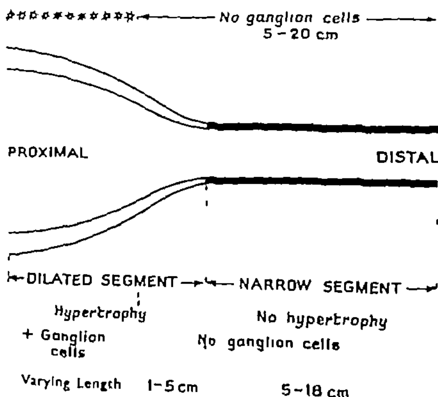


Fig 394—Schematic diagram of gross and microscopic changes in 15 cases of Hirsch sprung's disease with narrow segment. (W U neg 51 361) (From Bodian M: Lancet 1 6-11 1949)

Frozen section is a practical method of determining the absence of ganglion cells and should be used to determine the level of transection of the bowel at operation. This is a reliable method of diagnosis, for if the bowel is normal ganglion cells will always be present. We have checked the terminal rectum in patients without megacolon and ganglion cells have always been observed. There may be instances in which biopsy of the rectum should be done in order to establish the diagnosis (Swenson). In most instances however, the clinical signs and the radiographic findings should be sufficient to make a presumptive diagnosis of megacolon. The myenteric plexus is reported as absent in all cases of congenital megacolon in the most distal part of the colon (Whitehouse). Bodian states there is lack of parasympathetic function and coordinated propulsive movement of the distal segment. Operative treatment for intractable megacolon is resection of the segment of the colon in which ganglion cells are absent with preservation of the sphincter and the establishment of an upper colonic anal anastomosis.

TUBERCULOSIS

Most patients with secondary ulcerating tuberculosis of the colon do not require surgical therapy. Infrequently stenosing lesions particularly in the region of the cecum, accompany minimal pulmonary tuberculosis (Fuchs). Grossly the process involves the ileocecal area. There is ulceration with diffuse fibrosis extending through the wall causing contraction and obstruction (Inberg) (Fig 395). Microscopically the changes show typical tubercles and extensive desmoplasia. Surgical resection is usually curative although flare up of the pulmonary lesion may take place.

EXFOLIATIVE CYTOLOGY

Exfoliative cytology is of no value in the readily accessible carcinomas. Unfortunately in those carcinomas not accessible to biopsy by the proctoscope, exfoliated carcinoma cells are difficult to recognize because of degenerated changes. In a few rare cases in which a redundant sigmoid prevents adequate radiologic examination and biopsy cytologic study can determine the diagnosis. In a patient referred to us for study a colostomy had been done because of obstructive symptoms. No carcinoma could be recognized radiographically or by proctoscopy. Carcinoma cells were found, however in material obtained from the colostomy stoma, and operation confirmed the presence of cancer. Generally speaking exfoliative cytology is of little practical value in the diagnosis of cancer of the large bowel.

BIOPSY

Before radical surgery for carcinoma of the rectum and rectosigmoid area is undertaken a positive biopsy should be obtained. It is imperative that sufficient representative material be taken small wisps of tissue are not adequate. Although the gross pattern of a carcinoma is usually characteristic inflammatory lesions can simulate cancer and conversely innocent appearing small lesions may prove to be undifferentiated carcinomas. In the poorly differentiated malignant tumors there

is usually no difficulty in the diagnosis In the signet ring type of carcinoma only a few small islands of tumor cells may be present (Figs 417 and 418) It may be difficult to make a definitive diagnosis of carcinoma in a well-differentiated tumor without evidence of invasion, and an *endometrioma* may erroneously be called carcinoma unless the characteristic stroma is recognized The removal of tissue from



Fig 395 —Gross photograph of a constricting tuberculous lesion at the ileocecal valve occurring in a young man. There was almost complete intestinal obstruction Note extreme dilatation of the small bowel on the left with areas of tuberculous ulceration. After resection the patient completely recovered. (W U neg. 5? 3256)

the edge of an ulcerative carcinoma may show only hyperplastic colonic epithelium, and the lesion may be mistaken for an adenomatous lesion. Lymphoid polyp and lymphosarcoma may be difficult to differentiate. The cooperation of a surgeon skilled in taking tissue and an experienced pathologist makes the biopsy diagnosis of lesions of the colon almost 100 per cent accurate (Gabriel)

TUMORS

Adenomas

The common benign adenomas of the large bowel are tumors derived from epithelial cells Grossly these simple adenomas may be distributed throughout the

large bowel, but like carcinoma they are most frequently found in the rectum and rectosigmoid area. They may be sessile or pedunculated have a short or long stalk be multiple or single. They can be artificially divided into certain types but sharp distinction is not justified because one type shades into another

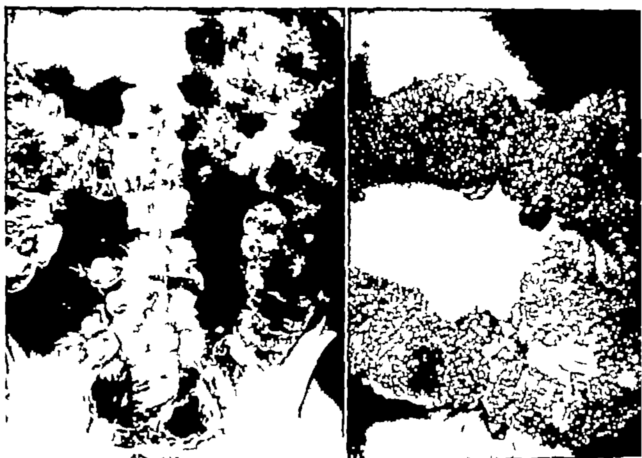


Fig 396 —Roentgenogram of familial polyposis of the entire bowel. (W U neg 49 1718)

Fig 397 —Gross photograph of extensive polyposis. There were four separate carcinomas present but fortunately all 265 regional lymph nodes were negative (W U neg 49 6546)

Familial polyposis of the large bowel is one entity which must be segregated from other adenomas. This inherited defect is a Mendelian dominant transmitted both by males and females. Adenomas in familial polyposis occur much earlier than the usual adenomatous polyp and in time one or more b cer Car cinomatous change in this lesion e twenty years ea ther cases of cancer usually in the early t ossly the bowel is ith polyps ranging anywhere from very sligh f the normal mu polypoid tumors malignant change is su ation or ulce e surface (Figs. 396 397 398, and 399) *adenoma* has ong stalk attached by a ra w base ary like proj s surf In the peduncul he pol form knob m. pattern of its ori diagra (Figs. 4

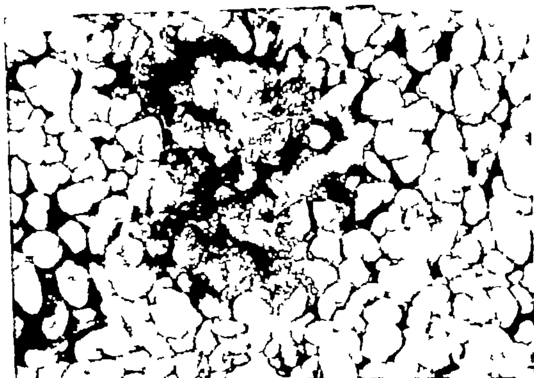




Fig 398 —Gross photograph of familial polyposis with an area of carcinomatous ulceration. (W U neg 49-6638.)

Fig 399 —Photomicrograph of minimal alterations in the surface glands of a polyp in a patient with familial polyposis. (×135) (W U neg 5? 2481)

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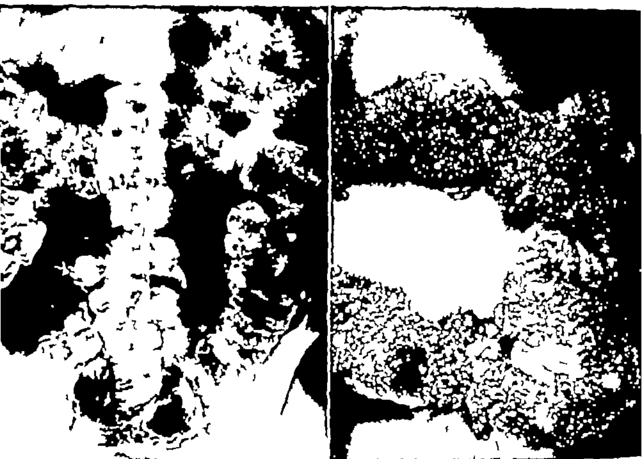


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Familial polyposis of the large bowel is one entity which must be segregated from other adenomas. This inherited defect is a Mendelian dominant transmitted both by males and females. Adenomas in familial polyposis occur much earlier than the usual adenomatous polyp and in time one or more become cancer Carcinomatous change in this lesion occurs some twenty years earlier than other cases of cancer usually in the early thirties. Grossly the bowel is studded with polyps ranging anywhere from very slight elevations of the normal mucosa to large polypoid tumors malignant change is suggested by fixation or ulceration of the surface (Figs 396 397 398 and 399) The *simple adenoma* has a short or long stalk attached by a rather narrow base and has papillary like projections on its surface In the pedunculated lesions the polypoid mass may form knoblike projections. The pattern of its origin has been diagrammed by Dukes (Figs. 400 and 401)

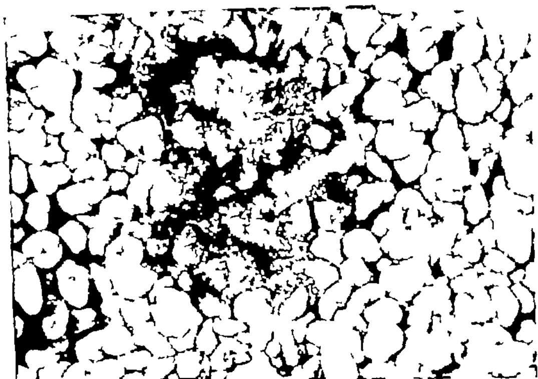
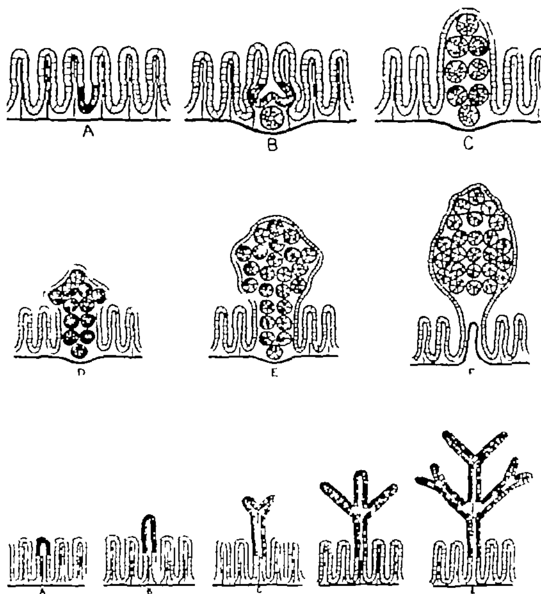




Fig 398 —Gross photograph of familial polyposis with an area of carcinomatous ulceration. (W U neg 49-6638)

Fig 399 Photomicrograph of minimal alterations in the surface glands of a polyp in a patient with familial polyposis. (×135) (W U neg 52 2481)

There is another type of adenoma which has had numerous names such as villous adenoma, but more recently it has been described as a *papillary adenoma* (Ewing Sunderland) This adenoma is usually single, occurs in older patients,



Figs. 400 and 401 —Dukes concept of formation of single adenoma. (Fig 400 W U neg 51 364 Fig. 401 W U neg 51 366.) (From Dukes C. E. Proc. Roy Soc. Med. 40: 829-830 1947)

Fig 402 —Dukes' concept of the formation of papillary adenoma. (W U neg 51 365) (From Dukes C. E. Proc. Roy Soc. Med. 40: 829-830 1947)

and is usually found in the rectosigmoid or rectal area. It eventually forms a large superficial neoplasm which may encircle the bowel. It has papillary villous projections and is usually attached by a wide base (Figs. 402 403 and 404) Microscopically these villous projections ramify through a long papillary crownlike

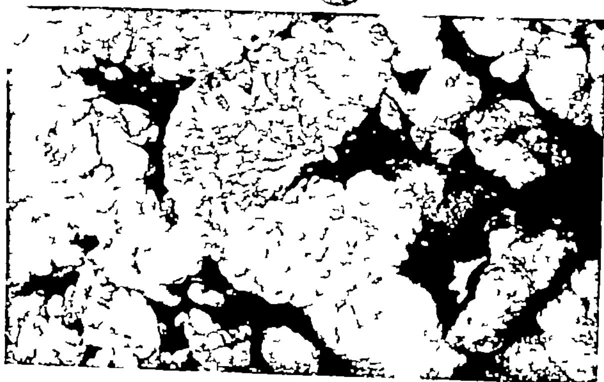


Fig 403 —Large papillary adenoma limited to the mucosa. (W U neg 51-6111)

Fig. 404 —This photograph shows the slightly magnified surface of the tumor illustrated in Fig 403 (W U neg 51-6110)





Fig 405 —Photomicrograph of papillary adenoma. (Low power) (W U neg. 49 4020)

Fig 406 —Photomicrograph of a papillary adenoma showing epithelium which is practically normal contrasted with epithelium which demonstrates nuclear changes with stratification and loss of polarity (×210) (W U neg 52 116.)



Fig 407 —Gross photograph of a single retention polyp in a child. Note cystic spaces. (W U neg 50-6790)

Fig 408 —Photomicrograph of the polyp shown in Fig 407 with overproduction of mucus and surface ulceration. This type of polyp does not become malignant. (Low power) (W U neg 51 144)

growth (Figs. 405 and 406) In time a high percentage of these lesions become malignant (Wheat) In children there is a type of polyp often designated as a *retention polyp* It is usually single and in the lower bowel (Helwig) Grossly it may be superficially ulcerated and on cross section has a cystic latticelike appearance (Fig 407) Microscopically it shows inflammatory changes on the surface and mucous containing cysts (Fig 408) This type of polyp rarely occurs in adults. The cystic or retention polyps occurring in childhood do not become malignant. These polyps may be sloughed and pass from the colon. It is unlikely that these lesions are true neoplasms (Horrilleno)

Evidence of Malignant Change in an Adenoma.—The adenoma of the large bowel may show all gradations of change from perfectly benign to obviously malignant and consequently it is sometimes impossible to be sure whether or not cancer is present In familial polyposis microscopic examination of the earliest lesions shows an epithelial surface which is distinctly different from normal epithelium (Fig 399) These changes include *stratification of the lining cells loss of nuclear polarity and interglandular budding* (Figs. 409 410 411 and 412) There is also a diminution in the capacity of these cells to produce mucin. With further advancement of the process the glands become smaller and show interglandular budding (Fig 413) with obvious carcinoma there are necrosis and invasion of the stalk of the polyp and of the deeper structures. In single or multiple adenomas of the large bowel and in familial polyposis the microscopic transitions from benign to malignant are the same. These alterations within an adenomatous polyp or papillary adenoma are as likely to occur in the tip as in the base. The fewer sections taken the less chance there will be of finding these alterations. We have taken step sections of an entire papillary adenoma and found focal areas of atypical change bordering on invasive cancer in only one small zone (Fig 414) It is certain that a high percentage of papillary adenomas become malignant.

Treatment.—There is no difficulty in the treatment of the cystic or retention polyps in children simple removal is sufficient. The surgical therapy of benign or borderline epithelial tumors of the large bowel requires judgment. All untreated patients with familial polyposis eventually develop carcinoma of the colon in the rectosigmoid or cecal zone. Therefore, even though the patient is young total colectomy is indicated If the rectum contains relatively few discrete polyps and the patient is cooperative ileoproctostomy may be performed and the polyps removed sigmoidoscopically (Coleman) These patients must be followed closely so that recurring polyps in the rectal segment may be removed. All adenomas should be removed and carefully sectioned

The treatment of adenomas is influenced by their location and the presence of a well-defined stalk. Adenomas below the peritoneal reflection can be removed through the proctoscope. If the stalk is free from cancer the patient is cured We have never seen metastases from an adenoma containing focal cancer in which the stalk was free from invasion. If the adenoma is located above the peritoneal reflection theoretically the best treatment is resection of the segment of bowel. Rarely colotomy with removal of the adenoma followed by frozen section is done.



Fig 409—Evacuation roentgenogram to demonstrate well-defined adenomatous polyp of the splenic flexure. (W U neg 48-6677)

Fig 410—Photomicrograph of cross section of normal glands in the adenoma shown in Fig 409 with some mitotic activity (×150.) (W U neg 48-6700)

Fig 411—Photomicrograph of adenomatous polyp shown in Fig. 409 with well-defined pedicle. There is no evidence of an infiltration of the pedicle by carcinoma. (Low power) (W U neg 48-6703)

Fig 412—Photomicrograph demonstrating deviation from the normal glands shown in Fig. 410 with stratification of nuclei and beginning loss of nuclear polarity (×150) (W U neg. 48-6701)



Fig 413 —Photomicrograph of early carcinoma with interglandular budding, stratification and loss of nuclear polarity The diagnosis of carcinoma was made only after reviewing all the sections of the biopsy Abdominal perineal resection of this sessile tumor showed extension into the wall of the bowel without metastases (×420) (W U neg. 52 2574)

Fig 414 —Photomicrograph of a small area of focal cancer found after subserially sectioning a papillary adenoma. (×380) (W U neg 50-2977)

If the stalk is free from cancer no further treatment is indicated Simple excision of small adenomas found incidentally on proctoscopic examination is curative (Fig 415)

Carcinoma

The evidence for the development of cancers of the colon from adenomas is in part based upon microscopic interpretation It is possible to demonstrate every histologic variant from a benign adenoma to invasive cancer within that adenoma



Fig 415—Photomicrograph of small adenoma of the large bowel without evidence of malignant change This is the type often seen on proctoscopic examination. Simple excision is usually sufficient. (Low power) (W U neg 51-6014)

In direct support of this hypothesis is the greatest occurrence of both in the rectosigmoid and cecal areas and the high frequency of colons removed for cancer However certain discrepancies exist. Helwig reviewed the intact colons from 1 460 consecutive necropsies in the Barnes Hospital and found 272 benign polyps and 25 manifest cancers More recently Spratt has studied specimens of 268 consecutive patients having colonic resections for single, multiple simultaneous, and multiple nonsimultaneous cancers of the colon. Statistical comparisons between the autopsy and surgical data showed the lack of certain correlations one might expect if all adenomas were cancer precursors. Colonic cancer occurred primarily in two areas of the colon 270 of 298 (90 6 per cent) of the clinical cancers, and 23 of 25 (92 per cent) of cancers found at necropsy were either in the rectosigmoid or in the proximal ascending colon or cecum. Less than 10 per cent of all colon cancers occurred in the 100 cm. of intervening colon Approximately 70 per cent of the cancers arose in the rectosigmoid colon This distribution was unaltered in patients with multiple simultaneous and nonsimultaneous cancers, and in

those with cancers and familial polyposis. Unlike colonic cancers, benign polyps, though most frequent in the cecal and rectosigmoid areas, were much more homogeneously distributed throughout the hepatic and splenic flexures, transverse colon, and descending colon. The lack of statistical correlation between the presence of adenomas and cancer in a long segment of the colon suggests that other factors may be important in the development of cancer in the colon. Other distributional discrepancies have been reported Hultborn found that 20 per cent of all colonic polyps occur in the rectum in contrast to the rectal site of 50 per cent of all colonic cancers. Spratt's study showed that if two colonic lesions were present, the most distal was usually cancer In other words if a patient with carcinoma of the rectosigmoid had a more proximal lesion it was benign (80 per cent of instances) The primarily cecal and rectosigmoid distribution of colonic cancer makes doubtful the value of prophylactic resection of all noncancerous intraabdominal colon as recommended by Lillihei and Wangensteen However this distribution must be kept in mind in the examination, treatment, and follow up of these patients.

The classification of carcinoma of the large bowel has little practical significance except for a few rare variants which have gross distinctions a divergent clinical course, and prognosis. The usual *adenocarcinoma* of the large bowel is a bulky tumor with well-defined rolled margins about an area of central ulceration There is a sharp dividing line between the carcinoma and the normal bowel wall (Fig 429) In rare instances intramural spread may be seen (Black) When these tumors are sectioned grayish white tissue replaces the bowel wall. In some, this replacement is well demarcated in others, fingers of tumor extend from the main mass. The pathologist should determine whether the tumor is confined to the wall or whether it has extended to the pericolic tissues. Large veins should be examined for gross vein invasion might rarely be seen (Dukes) If the tumor secretes a large amount of mucin, it has a mucoid glairy appearance, and lakes of mucin may separate the bowel wall. There is a rare type of carcinoma which is similar to the linitis plastica variant observed in the stomach (Laufman) This lesion exhibits poorly defined margins a pebbly mucosal surface which often is only superficially ulcerated (Figs 416-418)

Grading large bowel cancers has some merit in the evaluation of groups of cases (Dukes) Three grades are sufficient. Dukes divided his tumors into A, B and C categories A involves the wall of the bowel only B extends through the wall and C extends through the wall and has lymph node metastases. The most favorable type is the carcinoma confined to the mucosa and submucosa. However we agree with Dukes (1946) that extremely large tumors with no metastases often are successfully treated. These tumors are usually papillary adenomas with small areas of invasive cancer Small highly malignant tumors are fortunately rare. A high percentage of all carcinomas falls into the intermediate type. A rather small percentage of mucoid tumors are highly undifferentiated and should be classified as so-called signet ring type.

Examination of the Specimen —The method of examination of large bowel specimens as proposed by Dukes is probably the best. He fixes the specimen makes a diagram to scale and plots the distribution of the lymph nodes putting them in separate bottles Clearing the specimen is also accurate producing an

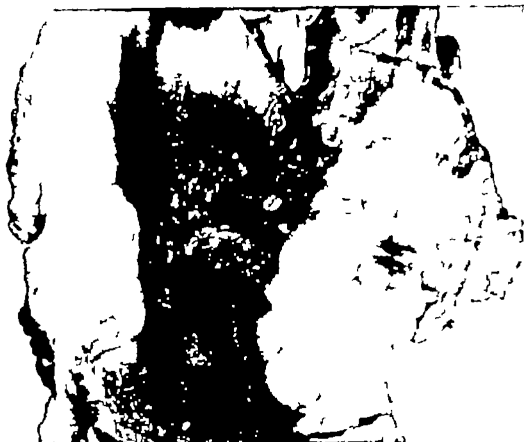




Fig 416 —Gross photograph of a carcinoma with signet ring cells This type is highly malignant, narrows the lumen and has a pebbly mucosal surface and thickened muscular wall. (W U neg. 51-4682.)

Fig 417 —Photomicrograph of biopsy of the carcinoma illustrated in Fig 416 which shows a small area effacing the glands (Low power) (W U neg 51 5362.)

Fig. 418 —Photomicrograph of the area illustrated in Fig 417 showing signet ring tumor cells. There were many lymph nodes involved in the surgical specimen.

average of at least fifty lymph nodes (Grinnell Coller) but we have found that such a time consuming procedure is not practical. Our modified method consists of opening the specimen, pinning it on cardboard and placing it in formalin After fixation at least three or four sections are cut from the primary tumor, these sections extend through the entire thickness of the wall The large veins are carefully examined and if there is any suggestion of tumor within them, sections are made. The nodes are dissected from the mesentery and divided into groups each group being placed in a separate bottle. The nodes below the tumor are also isolated these are obviously important nodes, for if tumor is found within them, the prognosis of the patient is probably hopeless inasmuch as retrograde involvement means blockage of lymph nodes at the tumor level. Likewise the lymph nodes at the high point of the dissection where the vessels are ligated are also separately examined for if tumor is found it means the disease has spread beyond the resection Lymph nodes are also removed from the region of the tumor and from the area between the tumor and the point of ligature. Sections are taken from other polyps or lesions noted in the bowel. At times each end of the specimen can be ligated after distending the bowel to about its normal lumen with 10 per cent formalin this serves to preserve the gross changes in the bowel in the same pattern as shown by roentgenogram This method is often helpful in demonstrating lesions other than carcinoma.

Microscopic Description.—The usual carcinoma of the large bowel is a well differentiated adenocarcinoma secreting variable amounts of mucin. In a few instances there may be extremely large lakes of mucin with scattered collections of tumor cells. The rare variant of the so-called linitis plastica type of carcinoma shows retention of the mucin for the most part within and compressing the tumor cells giving the nuclei a signet ring effect In a few instances areas of squamous change may be present We have seen such alterations in the cecal area and in the lower rectum (Figs. 419-421) It is important that for the main sections of the tumor stains be used which will demonstrate the presence or absence of vein invasion We use the Verhoeff van Gieson which stains smooth muscle yellow and brings out clearly the black elastic tissue. If vein invasion is demonstrated the prognosis is extremely unfavorable Also of prognostic importance is the presence or absence of nerve sheath invasion by the tumor and whether microscopic examination shows the tumor confined to the bowel wall or extending into the pericolic fat If there is tumor present in the lymph nodes, it is wise to examine the tissue in the immediate vicinity of nodes, for tumor frequently extends beyond the lymph node capsule to invade surrounding veins Rarely in slowly growing carcinomas of the rectum bone formation occurs (Dukes) We have seen several instances of local recurrence of colonic carcinoma at the suture line. Tumor has been apparently implanted on the raw surface at the time of operation. This was well shown in one case because tumor was present at the suture line, there was suture material intimately associated with the cancer and no involved lymph nodes were present. Methods of avoiding this complication have been described by Goligher and Cole

Prognosis in Carcinoma as Related to Pathologic Findings (Table 18).—The prognosis is excellent if carcinoma is discovered as an incidental finding in a polyp.

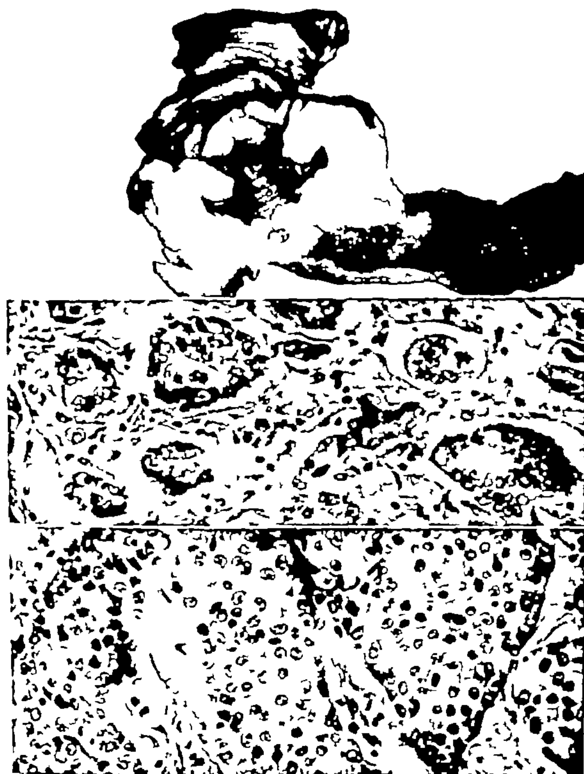


Fig 419 —Large ulcerating adenocarcinoma of the cecum with squamous metaplasia. (EFSCIL)

Fig 420 —Glandular area of tumor shown in Fig 419 (EFSCIL)

Fig 421 Zone of squamous change in tumor shown in Fig 419 (EFSCIL)

TABLE 18 PROGNOSIS IN CARCINOMA OF LARGE BOWEL BASED ON THE PATHOLOGIC FINDINGS

Excellent	1 Carcinoma in an adenoma without invasion of stalk 2 Carcinoma in a papillary adenoma limited to mucosa and submucosa 3 Carcinoma limited to mucosa and submucosa Only under exceptional circumstances do any of the above groups develop metastases
Good	1 Carcinoma limited to wall of bowel without lymph node metastases
Fair	1 Carcinoma with lymph node metastases limited to the immediate area of the tumor
Poor to Hopeless	1 Signet ring mucin-secreting carcinoma has an extremely poor prognosis (Laufman) 2 Extensive lymph node metastases 3 Gross or microscopic evidence of *vein invasion* 4 Microscopic evidence of nerve sheath invasion 5 Retrograde lymph node metastases (hopeless)
	Poor differentiation parallels invasiveness (see Table 19) and thereby metastases Exceedingly large carcinomas may have a favorable outlook (Dukes) Carcinomas located in the rectosigmoid area have a worse outlook than carcinomas located in the right colon Conservative surgical procedures prejudice cure Cure by radical surgery is still possible in the presence of fixation to other organs Vein invasion usually does not occur until the tumor has invaded the wall of the bowel

TABLE 19 RELATIONSHIP OF HISTOLOGIC GRADES TO INCIDENCE OF LYMPHATIC METASTASES (1 807 CASES)*

GRADE OF TUMOR	TOTAL CASES	CASES WITH METASTASES	PER CENT WITH METASTASES
Low grade	109	35	18.4
Average grade	1 162	515	44.3
High grade	455	356	78.2

*From Dukes C E.: J Clin Path. 2: 95-98 1949

TABLE 20 INFLUENCE OF LYMPHATIC SPREAD ON FIVE YEAR SURVIVAL RATE AFTER EXCISION OF THE RECTUM*†

	OPERATION SURVIVALS	ALIVE AT FIVE YEARS	PER CENT OF FIVE YEAR SURVIVALS
Cases without lymphatic metastases (A and B)	357	243	68.1
Cases with lymphatic metastases (C)	359	94	26.2

*From Dukes C. E. J Clin. Path. 2: 95-98 1949
†Based on all cases operated on at St. Mark's Hospital, 1928 to 1941 inclusive

If carcinoma occurs in a pedunculated adenoma and the stalk is not involved the prognosis is very good as there will be no metastases (Fig 422) The prognosis also correlates very well with Dukes classification in his Class A with the tumor confined to the mucosa and submucosa, the prognosis is excellent. With invasion of the wall the prognosis becomes less favorable, and with involvement of the lymph nodes the five year survival rate sharply drops. We have seen *small* highly undifferentiated carcinomas metastasize widely (Figs 423-426) Conversely we have seen circumferential carcinomas which were superficial, well differentiated, and without metastases With vein invasion the five year survival is

no more than 15 per cent Nerve sheath invasion is also a sign of advanced disease and usually is accompanied by other ominous pathologic findings In groups of cases, the higher the grade the worse the prognosis (Table 19) The location and extent of lymph node involvement are also significant, cures are possible when only those nodes in the immediate vicinity of the tumor are involved, the greater the number of lymph nodes involved the worse the prognosis (Table 20) If there is involvement of the lymph nodes in a retrograde fashion or if the tumor extends to the high point of the dissection, cure is practically never attained Retrograde



Fig. 422.—Photomicrograph of polyp with focal cancer The stalk is free from involvement and therefore the prognosis is excellent Inset shows an area of carcinoma. (W U neg. 58-253)

intramural spread of rectal cancer is fortunately rare. Quer studied 89 specimens and found retrograde spread in only 3 There is also some correlation between the location of the tumor within the bowel and prognosis Carcinomas of the cecum tend to be less invasive and have a lower percentage of lymph node metastases. The carcinomas of the rectum and rectosigmoid area more quickly infiltrate the wall and metastasize more frequently The type of operation also influences the outcome. An extensive resection of the tumor may cure certain persons who would die of cancer after less radical operations. Adequate surgery for cancer of the large bowel varies with its location. If cancer is located below the peritoneal reflection abdominoperineal resection is preferable to resections preserving the anus. For cancers in the cecal area, ileocolectomy is the operation of choice. When cancers are located in other portions of the bowel the operations must be of sufficient



Fig 423 Photomicrograph of small carcinoma of the rectum found on routine rectal examination There were metastases to many nodes, with blood vessel and nerve sheath invasion. (Low power) (W U neg 51 145)

Fig 424 Photomicrograph to demonstrate the undifferentiated carcinoma shown in Fig 423 (×435) (W U neg 51 151)

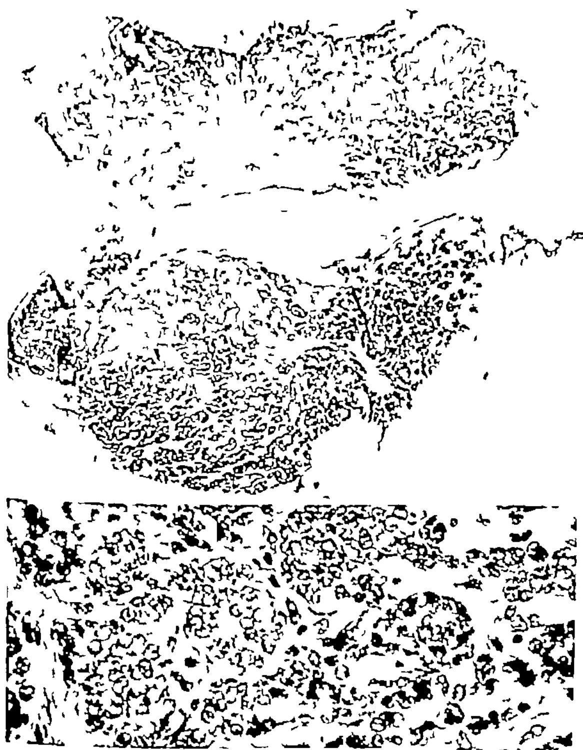


Fig 425 – Photomicrograph of generous biopsy of a small tumor of the rectum which proved to be carcinoma. (Low power) (W U neg 51 146.)

Fig 426 – Abdominoperineal resection was done No tumor could be found in the wall of the bowel but there were metastases in the regional lymph nodes. (×440) (W U neg 50-6472)

scope to obtain the potentially involved regional lymph nodes. We do not agree with Wangensteen that total abdominal colectomy is indicated for all cancers of the colon above the peritoneal reflection the chances of finding an undiscovered second tumor in the removed colon is not great enough to justify such a radical procedure.

Clinicopathologic Correlation in Tumors of the Large Bowel

Benign tumors may cause changes in bowel habits and occasionally bleeding either grossly or microscopically. Pedunculated and submucosal tumors may intussuscept. *Carcinoma of the large bowel often provokes diarrhea alternating with constipation.* Complete large bowel obstruction develops most frequently when the cancer is situated in the sigmoid or left colon. Perforation of the colonic wall may appear at the cancer site, but occurs more frequently in the cecum in the presence of an obstructing carcinoma of the left colon. The patient with carcinoma of the cecum or ascending colon typically presents without obstructive symptoms but with anemia due to chronic blood loss. It is imperative to follow all patients who have had a carcinoma or an adenoma because they have an increased chance of developing a second tumor (Figs 427-430).

Lymphosarcoma

Lymphosarcoma is less frequently found in the large bowel than in the small bowel or stomach but we have seen it in every portion of the large bowel. In some areas the tumor may produce prominent mucosal folds in other zones, distinct nodules or prominent ulceration. This tumor may form a large mass grossly and on section extremely cellular gray tumor may be seen replacing muscle walls. Frequently there are large involved regional lymph nodes having the same characteristics as the primary tumor. The microscopic pattern varies to include all types of lymphosarcoma. It is rarely curable. We have not seen Hodgkin's disease involve the large bowel although it has been reported by others.

Lymphoid Polyp (Benign Lymphoma)

Lymphoid polyps may infrequently be found in the rectal area. They are soft superficial polyps usually covered by an intact gray smooth mucosa. In Helwig's series 40 were single and 25 were multiple. These submucosal lesions are made up of lymphoid tissue with follicle formation a lobular pattern, and reaction centers (Fig 431). The tumor may distort the muscularis mucosae but does not extend into the muscularis propria. A superficial or small biopsy could be incorrectly diagnosed as lymphosarcoma. The patient may complain of a mass, bleeding or prolapse. Local excision is curative.

Carcinoid Tumors

Carcinoid tumors of the large bowel are rare malignant neoplasms arising from argentaffin cells (Horn Pearson). They occur in any portion of the large bowel, tend to be large extend deeply through the wall of the bowel and involve



Fig. 427.—Roentgenogram taken in 1929 demonstrating carcinoma of the transverse colon. This was successfully removed. (W U neg 51-6081)

Fig 428.—Roentgenogram taken in 1951 demonstrating new carcinoma in region of splenic flexure. (W U neg 51-6082)

Fig 429.—Gross photograph of tumor seen in the roentgenogram taken in 1951 (W U neg 51 5695)

Fig. 430.—Gross photograph of a small adenomatous polyp in close proximity to the large carcinoma shown in Fig 429 Figs. 427-430 illustrate graphically the necessity of follow-up on patients with adenomas or carcinomas of the large bowel. (W U neg 51 5694)

Fig 431 —Photomicrograph of a lymphoid polyp of the rectum. Note intact overlying mucosa lobular pattern, and reaction centers. (*Low power*) (W U neg 51-6015)

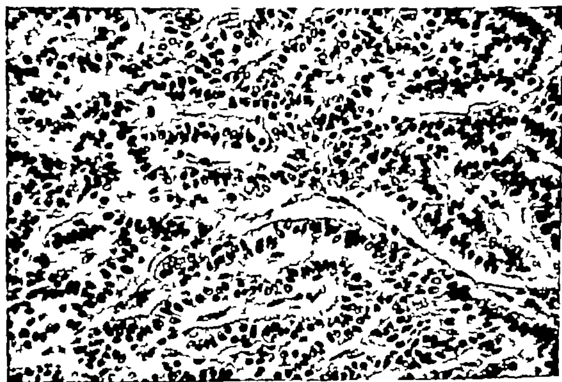
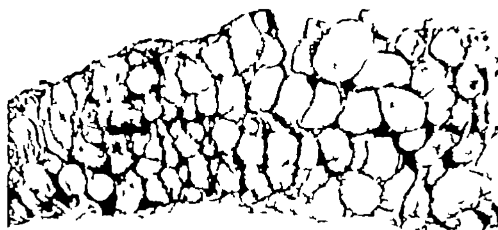


Fig 432 —Photomicrograph of carcinoid tumor of the rectum. Note the typical pattern of festoons and ribbons. (×235) (W U neg 51 1222)





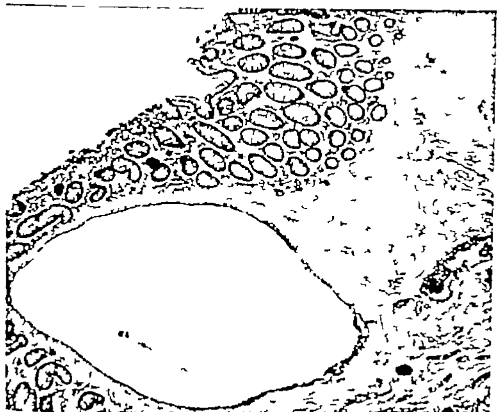


Fig. 433—Two gross photographs demonstrate polypoid grapelike masses formed by submucosal gas cysts. Photomicrograph of the biopsy shows one of these small cysts surrounded by granulomatous changes in the stroma. (Low power.) (W. U. negs. 54-6278, 54-6279 and 55-587.) (From Ramos, A. J., and Powers, W. E.: Am. J. Roentgenol. 77: 678, 1957.)

the regional lymph nodes. They often have a light yellow color Because they may be multiple, search should always be made for submucosal satellite tumors. Microscopically they have the typical pattern of a carcinoid neoplasm. Some tumors reduce silver but others do not. Stout has designated the latter as being in a pre-enterochrome phase. They may be arranged in festoons and ribbonlike masses (Fig 432) The growth rate is usually slow so that it is worth while to do a palliative procedure even in the presence of advanced disease. In the rectum they are usually small often on the anterior wall and if found at an early stage of development may be cured by local resection (Epps)

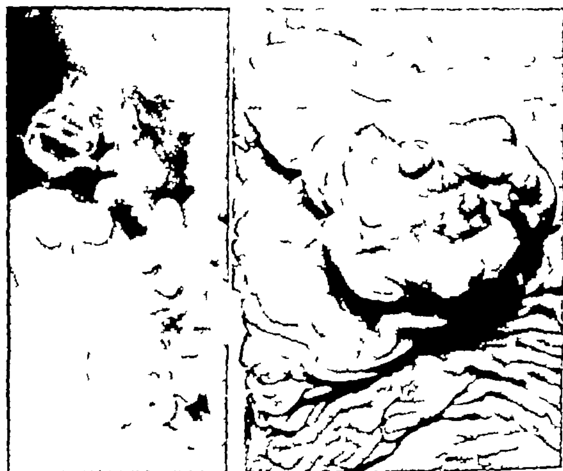


Fig 434 —Roentgenogram to show filling defect in the region of the cecum caused by a lipoma. (W U neg 48-3832.)

Fig. 435 —Gross photograph of the submucosal lipoma producing the filling defect in Fig 434 (W U neg 48-3831)

Rare Lesions

Barium granulomas of the rectum and perirectal tissues can occur following barium enema. Barium escapes through a break in the mucosa produced by in fection, tumor foreign body or trauma. The barium provokes a granulomatous reaction and the crystals may be seen under polarized light (Beddoe) *Pneu matosis cystoides intestinalis* may occur rarely in the large bo l produce signs of intestinal obstruction, and lead to an incorrect radiogr + osis of cancer

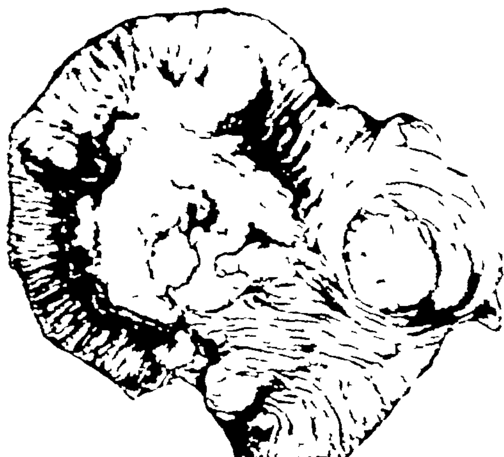


Fig. 436.—Gross photograph to show metastatic carcinoma involving the bowel. Note uninvolved mucosa extending right up to the point of ulceration.



Fig. 437. Gross photograph of localized endometriosis of the sigmoid producing almost complete obstruction. (W U neg 53-576[illegible])

Grossly this lesion shows polypoid grapelike masses formed by submucosal gas cysts (Fig 433) Biopsy of the case shown in Fig 433 demonstrated a submucosal cyst and granulomatous changes in the stroma These changes are diagnostic (Ramos) Endometriosis rarely may cause enough involvement of the large bowel to produce almost complete obstruction The presence of endometrial tissue within the wall of the bowel causes secondary smooth muscle hypertrophy (Fig 437)

Lipomas of the large bowel are rare invariably are submucosal and therefore may intussuscept (Mayo) (Figs. 434 and 435) Occasional *leiomyomas* and *leiomyosarcomas* have been reported (Golden) *Metastatic malignant tumors occur* as a part of a disseminated process. These tumors form disclike areas in which there is a central area of ulceration but the mucosa extends right up to the point of ulceration giving indirect evidence that it was first a metastasis in the submucosa (Fig 436) We have seen this occur particularly in malignant melanoma, lymphosarcoma and primary carcinoma of the lung

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Rare Lesions

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ANUS

EMBRYOLOGIC DEFECTS

Anomalous connections between the rectum and urinary tract and between the rectum and the genital tract can occur on an embryologic basis (Crowell). In early embryonic life the rectum is separated from the anus by the anal membrane which, if it persists, results in an imperforate anus. At times this imperforate anus may be accompanied by a fecal fistula (Ladd). Imperforate anus with or without perineal or genitourinary tract fistula constitutes the only important congenital defect of the anus. Before operation it is mandatory that cystograms be done. There may be obstruction distal to a urinary tract fistula so that complete urinary retention may follow repair of the imperforate anus. The treatment of most infants with imperforate anus requires an abdominal operation to ensure adequate mobilization of the rectum to allow mucocutaneous approximation without tension (Ladd).

The closed anal canal is thrown into folds (columns of Morgagni). The upper ends of the columns are connected by the semilunar valves which form the inner boundary of minute pockets known as the crypts of Morgagni (Fig 438). Between the semilunar valves are toothlike raised projections called anal papillas. The anal ducts course downward and outward and often extend into but not through the internal sphincter (Dunphy, Kratzer) (Fig 439). Infection in a crypt involves the anal ducts from which it may spread to produce a perianal or ischiorectal abscess.

FISSURE IN ANO

An anal fissure is a single linear separation of the tissue of the anal canal extending through the mucous membrane. Ninety per cent of anal fissures are found at the posterior commissure overlying the bifurcation of the sphincter as it divides to circle the rectum. An anal ulcer is a chronic fissure usually oval in shape which extends into the muscular layer. Above it is a hypertrophied papilla, and behind this papilla is an infected crypt. External to the ulcer is a skin tag, the result of chronic edema and fibrosis surrounding the ulcer. Granvalsky has

seen carcinomas that he believes arise from anal glands. He indicates that these neoplasms arise outside the anus and rectum but subsequently produce a bulging mass into the lumen Furthermore he believes that a segment of mucosa inter



Fig 458 —Gross photograph of a normal lower rectum and anus illustrating the mucocutaneous junction the semilunar valves and the crypts of Morgagni. (W U neg. 52 565)

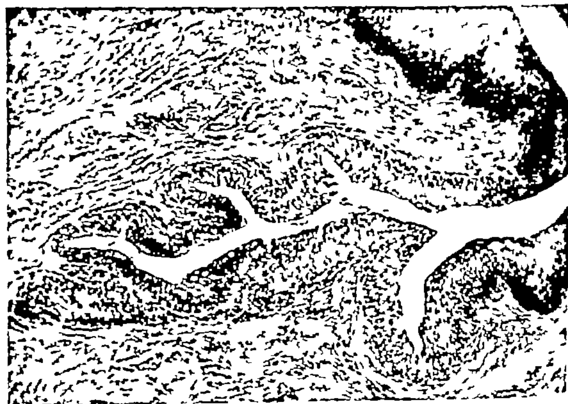


Fig 459 —Photomicrograph of a normal anal gland. It is penetrating into the muscle and is lined by both stratified squamous and mucus-secreting cells. (×110) (W U neg 51 5610)

posed between rectum and anus has structural characteristics that make it acceptable as a remnant of cloacal entoderm Such an anatomic explanation would explain the wide variation of histologic patterns seen in cancers involving the anorectal junction.

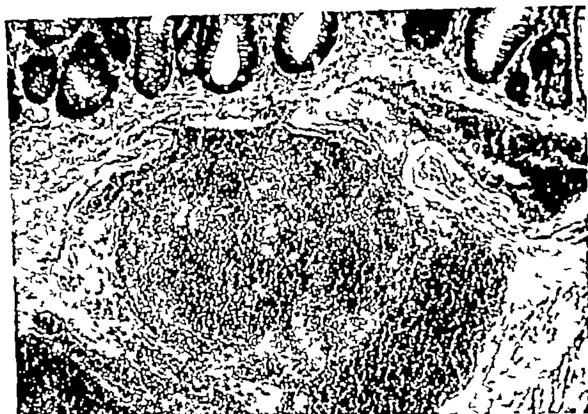


Fig. 440—Photomicrograph of a small submucosal hemorrhoid just within the anus. (Low power) (W U neg 52 2571)

HEMORRHOIDS

Stasis of blood in the veins of the hemorrhoidal plexuses is usually due simply to dependency However pathologic processes in the drainage path of those veins may cause secondary engorgement. Therefore the presence of hemorrhoids may be an indication of some other process such as cirrhosis of the liver with portal hypertension carcinoma of the rectum leiomyoma of the uterus or pregnancy Hemorrhoids can be present either within or outside the anus. Thrombosis within these dilated veins is common (Fig 440) If the cause of venous obstruction is removed the hemorrhoids may disappear although in many instances surgical resection is necessary

EPIDERMOID CARCINOMA

This infrequent carcinoma may occur on a basis of a chronic nonspecific inflammatory process (Skir) and with specific processes such as lymphopathia venereum (Binkley) (Fig 447) Grossly this carcinoma appears near the mucocutaneous junction and grows either upward into the rectum and surrounding tissues or outward to the perianal tissues (Figs 441 443) At times the growth

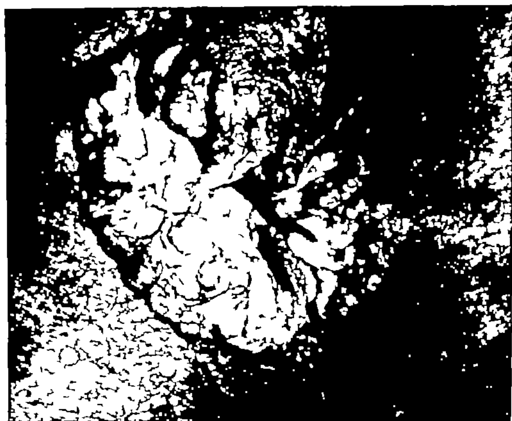


Fig 441.—Clinical photograph of an anal epidermoid carcinoma extending into the perianal area. (W U neg 49-3917.)

Fig. 442.—The tumor shown in Fig 441 was irradiated with excellent temporary results. (W U neg 48-1714.)

Fig 443.—Tumor locally recurred, and abdominoperineal resection was done. Note irradiation effect in skin and narrowed anal canal. (W U neg 50-1350.)

Fig 444.—Persistent tumor remained. Note the plexiform pattern and the palisading of cells around the border. The regional lymph nodes were negative. The patient died of disseminated disease four years following microscopic diagnosis. (×200.) (W U neg 50-695.)



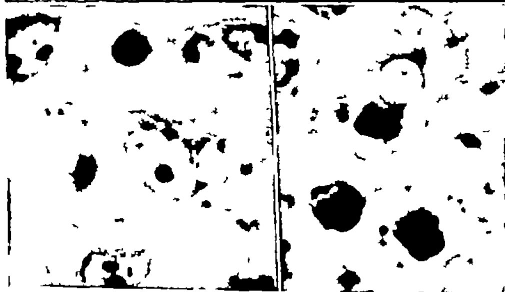


Fig 445 —Clinical photograph of granuloma inguinale simulating a carcinoma. (W U neg 48-4599)

Fig 446 —Photomicrograph of Donovan bodies in cytoplasm in patient with granuloma inguinale (High power) (W U neg 47 3907)

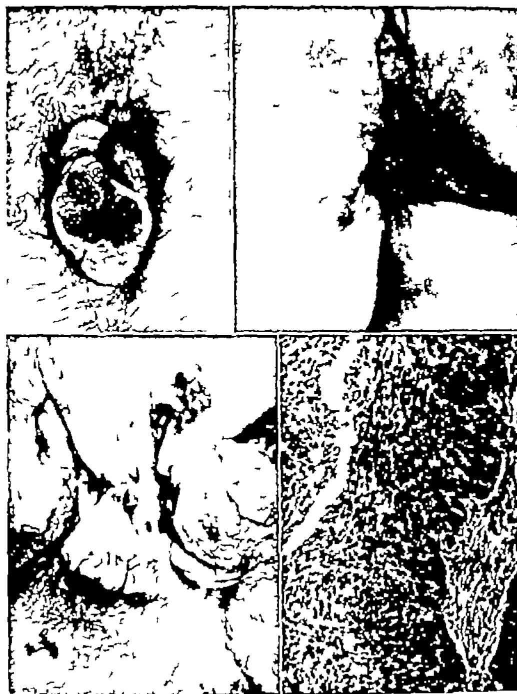


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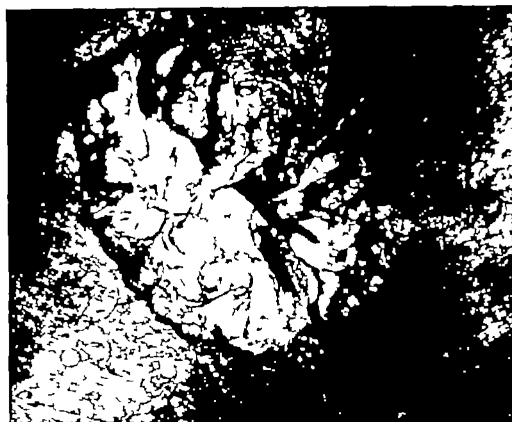




Fig. 445 —Clinical photograph of granuloma inguinale simulating a carcinoma. (W U neg 48-4599)

Fig 446 —Photomicrograph of Donovan bodies in cytoplasm in patient with granuloma inguinale. (High power) (W U neg 47 3907)

almost exactly simulates an adenocarcinoma of the rectum, and the correct diagnosis is made only with biopsy Involvement of the perianal skin may be superficial with only surface ulceration and slightly elevated margins. Such lesions have been mistaken for an unusual inflammatory process In other instances a typical deeply ulcerated neoplasm with rolled edges is seen. These squamous

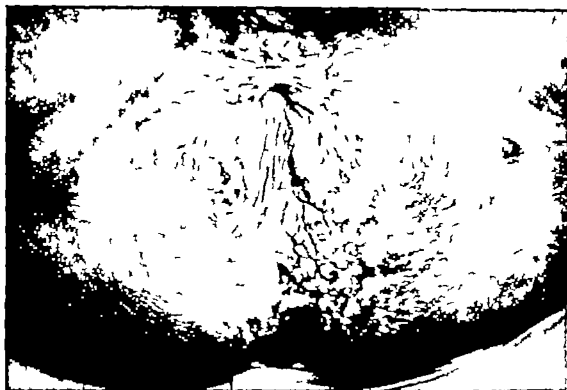


Fig 447 —Clinical photograph of lymphopathia venereum with epidermoid carcinoma. The Frei test was positive. (W U neg 5? 3301)

carcinomas are poorly differentiated microscopically The superficial type resembles a basal cell carcinoma (Fig 444) but this variant metastasizes. Local extension upward of the growth may burrow beneath the overlying epithelium only to ulcerate at a higher level. Dukes reported five tumors in which the upper portion was adenocarcinoma and the lower portion squamous carcinoma. Because of the dual lymphatic spread from the pectinate line regional lymph nodes along the rectum or in the inguinal areas may be involved. A small number of these tumors are cured by abdominoperineal resection followed by bilateral radical groin dissection (Sweet) However if the inguinal lymph nodes are involved, prognosis is extremely poor (Judd) Tumors growing predominantly on the anal skin have been cured by irradiation (Meland) True basal cell carcinomas can occur at the anal margin and can be cured either by local excision or irradiation (Wittoesch) We have seen granuloma inguinale confused with epidermoid carcinoma (Fig 445) Biopsy in such cases will exclude carcinoma. A definite diagnosis of granuloma inguinale can be made if Donovan bodies are found (Fig 446) Patients with long standing lymphopathia venereum with associated rectal stric

ture are prone to develop squamous metaplasia of the rectum and epidermoid cancer (Rainey) Mucoid cancer is rarely a complication of long standing fistula in ano (Rundle)



Fig 448 —Gross photograph of malignant melanoma growing upward into the rectum to form a polypoid mass. There were innumerable metastases. (W U neg 50-4182)

MALIGNANT MELANOMA

Patients with melanoma occurring in the anal region rarely have noted a previous pigmented mole. The tumor often begins at the pectinate line and grows upward into the rectal ampulla. Multiple polypoid masses may form and grow beneath the intact mucosa (Chalier) (Fig 448) Because they are polypoid and smooth, they look benign (Raven) Microscopically they are similar to those described under Skin (see page 122) The prognosis is invariably hopeless.

RARE TUMORS

Hidradenomas may arise from apocrine sweat glands in the region of the anal canal (Teloh) and epidermoid cysts in the region of the anus (Bonser) Pseudotumors may be produced by sclerosing agents used to obliterate hemorrhoids.

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Chapter 10

MAJOR AND MINOR SALIVARY GLANDS

DISTRIBUTION OF SALIVARY GLAND TISSUE

Salivary gland tissue probably is best discussed as a whole rather than according to its anatomic location. The major salivary glands are the parotid, submaxillary and sublingual. The parotid is the largest, the submaxillary is about one fourth its size and the sublingual is about one third the size of the submaxillary. The main duct of the parotid gland (Stensen's duct) empties into the oral cavity on the buccal mucosal surface. The ducts of both the submaxillary and sublingual glands open in the floor of the mouth. Salivary gland tissue is also present in many other locations. In these locations it can give rise to benign

tumors, to inflammatory conditions and to malignant tumors. The location of the salivary gland tissue, to some extent influences the clinical signs and symptoms, the pathology and treatment Salivary gland tissue can be found in the lips, more commonly in the upper than lower lip, and is found throughout the oral cavity Mucous glands are found in the buccal mucosa the gum floor of the mouth the hard palate the soft palate the tonsillar areas, and in the tongue itself The lacrimal gland may be the site of salivary gland tumors Tumors similar to those found in major salivary gland tissue occasionally arise from the mucous-secreting glands of the trachea and bronchus, and the lining cells of the sinuses can give rise to tumors similar to those found in the major salivary gland tissue. Heterotopic salivary gland tissue can be found in lymph nodes within or near the parotid gland in newborn infants and can also be present in the adult (Brown) Tumors of salivary gland origin can be produced experimentally and in mice where they *appear to arise from the epithelial cells of the intercalated ducts (Bauer)*



Fig 449—Large radiopaque calculus within the submaxillary gland. (W U neg 48-4631)

CALCULI IN SALIVARY GLAND DUCTS

Calculi can form in the major ducts of the submaxillary sublingual and parotid glands. These laminated calculi without a foreign body or bacterial nidus are composed of a crystalline component apatite (complex phosphate compounds) identified as carbonate apatite (Blatt) (Fig 449) The stones are more frequently found in the submaxillary gland ducts than in the parotid gland ducts because the saliva is more supersaturated in calcium salts (Husted) With the formation of calculi there is block of secretion and swelling of the salivary gland tissue If this block continues there is frequently destruction of acinar tissue, and inflammatory induration in the region of the salivary gland. In the blockage of the ducts of the submaxillary and lingual glands tremendous induration can occur in

the floor of the mouth which on palpation may be mistaken for neoplasm The salivary gland duct orifices become erythematous and swollen Radiologic examination, including sialography may demonstrate radiopaque obstructive masses. Microscopic examination of glands which have been secondarily affected by stones shows dilation of ducts at times squamous metaplasia of the epithelium, moderate to prominent chronic inflammation, and a variable destruction of acinar tissue (Fig 450) We have seen one instance in which there were numerous almost microscopic stones within small ducts with subsequent atrophy of the lobules This process occurred in both parotid glands.



Fig 450 —Photomicrograph of submaxillary gland demonstrating minimal dilatation of the ducts acinar atrophy and chronic inflammation. There were small stones in one of the ducts leading to this area (×150) (W U neg 57 3460A.)

IRRADIATION

In irradiation of tumors of the oral cavity the submaxillary gland is often included in the field of irradiation The submaxillary glands swell and become firm (Fig 451) Microscopic examination shows decrease of acinar elements and increase of chronic inflammatory cells in the interstitial tissue (Fig 452) The lining of the duct epithelium may become squamous Such changes are often clinically mistaken for metastatic carcinoma and radical therapy such as bilateral upper neck dissection is done (Evans)

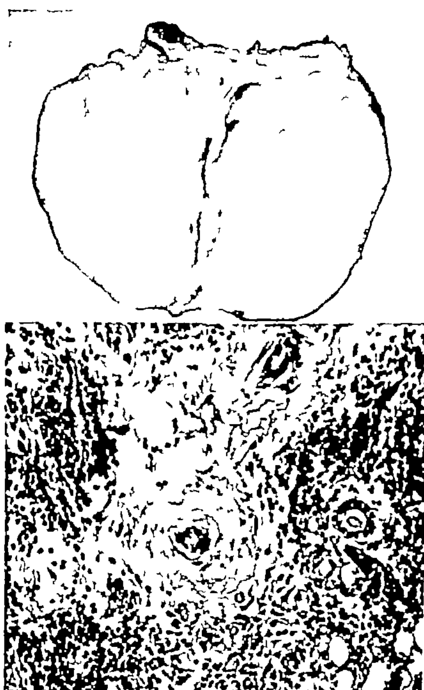


Fig. 451.—Gross photograph of fibrosis of the submaxillary gland related to irradiation. Note obliteration of normal pattern of the salivary gland. (W U neg. 51 5879.)

Fig. 452.—Photomicrograph of irradiation effect of the submaxillary gland. Note persistence of ducts, absence of acinar tissue, and presence of chronic inflammatory cells. (×250.) (W U neg. 50-686.)

MIKULICZ DISEASE

Mikulicz syndrome may be caused by a variety of conditions including lymphosarcoma, tuberculosis, sarcoid, and even syphilis. Mikulicz disease is an extremely vague entity (Schaffer). This disease consists of asymptomatic swelling of all or any combination of parotid, submaxillary, sublingual, and lacrimal glands. This

swelling slowly increases and the clinical enlargement is quite striking If the patient develops an infection the process subsides only to recur later It is a benign process often terminating in about five years The microscopic picture has not been well described As Morgan indicates, *Mikulicz disease is not a distinct* clinical and pathologic entity, but merely one manifestation within the generalized symptom complex known as Sjögren's syndrome. This syndrome includes swelling of the parotid salivary gland and rarely sublingual and submaxillary glands The glands show preservation of normal lobular architecture, diffuse enlargement, and replacement of acinar parenchyma by lymphoid tissue. Most important diagnostically is the formation of epimyoepithelial islands within the ducts (Fig 453) There is often associated keratoconjunctivitis xerostomia, and rheumatoid arthritis.

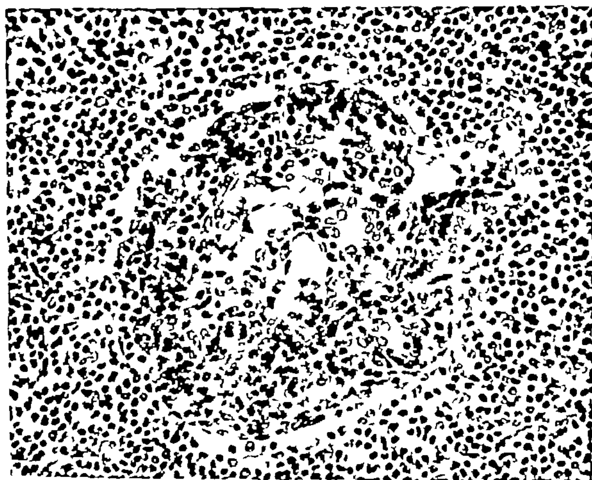


Fig 453 —Photomicrograph of prominent myoepithelial proliferation of duct epithelium in patient with Mikulicz disease. (×370) (W U neg 57 3679A.) (Slide contributed by Dr Benjamin Castleman, Massachusetts General Hospital, Boston, Mass)

TUMORS OF SALIVARY GLANDS

Benign Tumors

Hemangioma.—Hemangiomas of the salivary gland usually occur in the parotid gland and are often present in children where they form a diffuse soft mass without fixation to the overlying surface This lesion is a congenital malformation and apparently diffusely involves the parotid gland Microscopically it is made up

of anastomosing thin walled capillaries (Fig 454) These lesions have been treated by surgery or by judicious small amounts of radiation They do not become malig nant (Caldwell McFarland)

Lipoma and Neurilemoma.—Diffuse lipomas may involve the region of the parotid salivary gland A rare tumor, the neurilemoma is a specific tumor of nerve sheath origin, and can at times arise from one of the fine radicals of the facial nerve and be present in the region of the parotid salivary gland. (See Soft Tissue Tumors for detailed description) This tumor is a perfectly benign en capsulated neoplasm which often is incorrectly diagnosed as sarcoma when it occurs in the region of the parotid. Failure to recognize this tumor as a benign neoplasm may result in needless sacrifice of the facial nerve (Roos) We have now seen two instances in which the facial nerve has been sacrificed for this benign neoplasm.

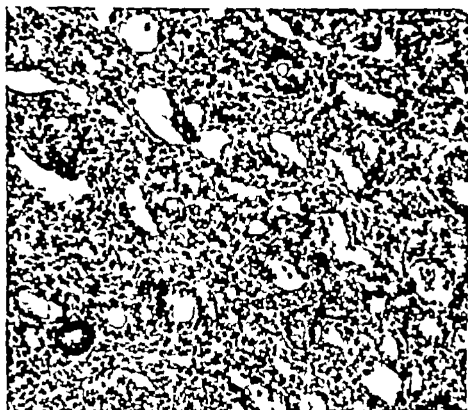


Fig 454 —Photomicrograph of a capillary hemangioma involving the parotid salivary gland in a child Cellular hemangioma replaces salivary gland, but ducts can still be seen. (×210) (W U neg 50-688)

Oxyphil Adenoma (Oncocytoma) and Papillary Cystadenoma Lymphomatosum (Warthin's Tumor)—These two benign neoplasms should be discussed together because of their common histogenesis. Both the oxyphil adenoma and the papillary cystadenoma arise from duct epithelium. In the developmental embryology of parotid and submaxillary glands, the parotid gland shows con siderable lymphoid tissue and the submaxillary gland does not (Thompson) Both oxyphil adenoma and papillary cystadenoma lymphomatosum are infre quently bilateral neoplasms. The oxyphil adenoma used to be described as an

oncocytoma (Hamperl Ackerman) However oxyphil adenoma is a better name (Meza-Chavez) These neoplasms grow slowly and do not become large. On microscopic examination they are composed of large cells well-defined nuclei, and granular cytoplasm (Fig 455) Mitotic figures are absent and cellular transition from normal lining cells of the ducts is seen Simple excision is all that is necessary They do not become malignant and only rarely recur if incompletely removed. The differentiation between hyperplasia and tumor may be difficult Cells of this type increase in number with age Although these tumors are predominantly within the parotid salivary gland we have also seen such lesions within the submaxillary gland We have seen focal hyperplasia of oxyphil cells clothing lymphoid aggregates in the region of the tonsil on two occasions and on the buccal mucosa on one occasion. These three lesions were not true neoplasms but formed localized nodules suggesting tumor

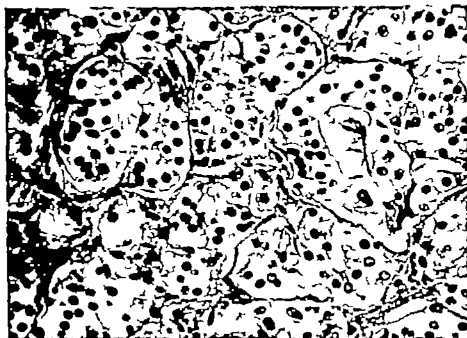


Fig 455 —Photomicrograph of an oxyphil adenoma of the parotid gland with large cells, granular cytoplasm and uniform nuclei. These benign tumors arise from duct epithelium. (×400) (W U neg 52 2572)

Papillary cystadenoma lymphomatosum arises from the ducts. It is a tumor which does not become large and may involve both glands (10 per cent of cases) It does, however become cystic, and occasionally it may become fixed to the overlying skin surface and be mistaken for a malignant neoplasm On cross section it forms a cystic mass. Between the fluid filled cystic spaces grayish lymphoid tissue can be seen (Fig 456) Microscopically there is prominent lymphoid tissue present often with germinal centers and covering the surface of this lymphoid tissue are large cells with granular cytoplasm similar to the cells seen in an oxyphil adenoma (Fig 457) There have been cases reported in the submaxillary gland but it is probable that these represent tumors arising from the mandibular extension of the parotid salivary gland Simple excision of these neoplasms is all that is necessary (Thompson Meza-Chavez)





Fig 456.—Gross photograph of a circumscribed papillary ... of the parotid gland. The tumor had a brownish-gray color due to the presence ... tissue. There are small cystic spaces present. (W ... 2950)

Fig 457.—Photomicrograph ... pillary cystadeno ... the lining large ... Lymphoid tissue with germinal centers ... Low power.) (W U neg 48-6470)

Mixed Tumors

Mixed tumors are the commonest group of neoplasms of salivary gland origin (see Table 15) Their incidence in the different salivary glands is directly proportional to the volume of the gland. These neoplasms are most frequent in females around the age of 40 but are also seen in children (Byars) and in aged adults of either sex.

Grossly the mixed tumor forms a rubbery resilient mass with a bosselated surface and may grow to a large size (Figs 458-460) Its consistency depends on the presence of cartilage and the degree of cellularity Extensions of tumor invade the normal salivary gland tissue On section it has a somewhat glistening mucoid appearance with cellular areas and at times zones of apparent cartilage.



Fig 458 —Gross photograph of external and cut surface of a large benign mixed tumor of the parotid salivary gland The cut surface shows areas of cystic change and the external surface has a typical bosselated appearance (W U neg 55-4349)

Bone is extremely rare. The histogenesis of these epithelial tumors appears to be well established not only by histologic study but by tissue culture (Favata) Microscopically there is no neoplasm which is so frequently incorrectly diagnosed as carcinoma by the neophyte in pathology The bewildering pattern the extreme cellularity the invasion of the capsule by the neoplasm all make it most confusing The typical tumor is made up of glands which mimic the normal tubules of the gland These glandular structures often have a double layer (Fig 461) In the extremely well-differentiated tumor keratinized epithelial plugs may be present within the lumen There is a characteristic mucoid myxomatous stroma which may develop into cartilage. This true cartilage developing from the connective tissue stroma is thought by Yates to be related to an organizer effected by the epithelial elements.





Fig 456 —Gross photograph of a circumscribed papillary cystadenoma of the parotid gland. The tumor had a brownish-gray color due to the presence of lymphoid tissue. There are small cystic spaces present. (W U neg 5? 2950)

Fig 457 —Photomicrograph of typical papillary cystadenoma lymphomatosum. Lymphoid tissue with germinal centers occurs beneath the lining large oxyphil cells. (Low power) (W U neg 48-6470)

Mixed Tumors

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Two types of mucin may be formed epithelial mucin from the glandlike areas and mesodermal mucus from the stroma (Grishman) The mixed tumor may also show areas of extreme cellularity (Fig 462) In the benign group however there is only a rare mitotic figure and no evidence of necrosis.



Fig 459 —Clinical photograph of a benign mixed tumor of the parotid salivary gland of long duration. There was no ulceration or facial nerve paralysis. (W U neg 50-3146.)

Fig 460 —Gross photograph of the tumor shown in Fig 459 Note variegated appearance with areas of mucoid change and cartilage-like material. (W U neg 50-3147) (Courtesy Dr John Modlin Ellis Fischel State Cancer Hospital, Columbia Mo.)

The *recurrence rate* of the mixed tumor depends on many factors the most important of which is the surgical treatment. A high percentage of the recurrences appears during the first year following surgery and with recurrence the

hances of further recurrence are high (25 per cent) (Frazell) If the surgeon nucleates the tumor small remnants of mixed tumor will be left behind and in ime perhaps after many years it will recur If the surgeon cuts through the

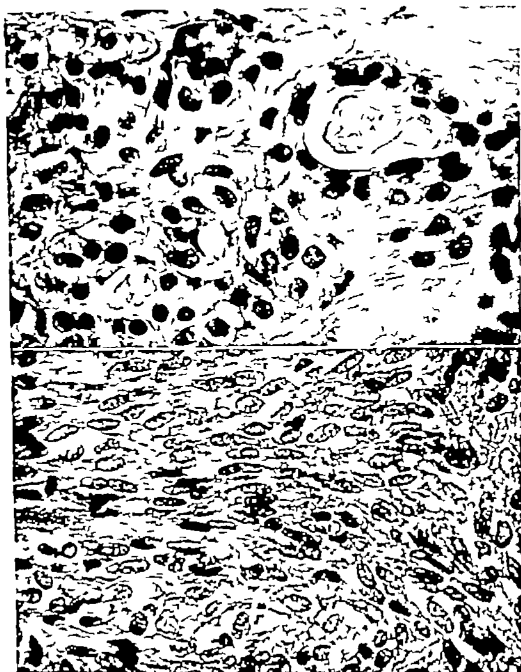


Fig 461—Photomicrograph of ductlike structures within a mixed tumor Note the double cellular layer (×380) (W U neg 51-801)

Fig 462—Photomicrograph of an area of prominent cellularity in mixed tumor Such changes may be mistaken for malignancy (×360) (W U neg 51-802)

mixed tumor with his knife he may implant it in the wound We have seen such recurrences on numerous occasions In mixed tumors there may be threadlike ramifications to other nodules so that the surgeon may cut through these threads, leaving behind small satellite nodules from which a recurrence may take place

The microscopic pattern of the tumor is of practically no significance in estimating whether a given mixed tumor will or will not recur. The surgical removal must encompass the tumor so that there will be a margin of normal salivary gland tissue around its extracapsular removal. With this method of attack there will be practically no recurrences.

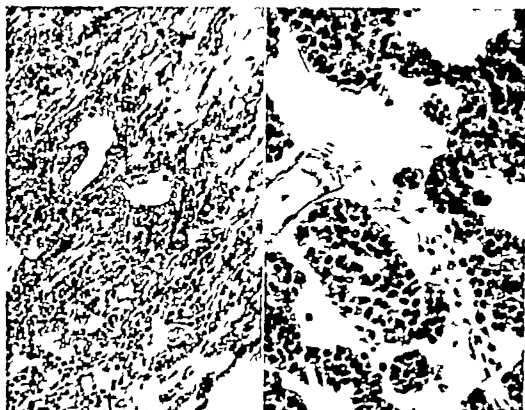


Fig. 463.—Photomicrograph of a benign mixed tumor with typical microscopic pattern. (×200.) (W.U. neg. 5? 2575.)

Fig. 464.—Photomicrograph of the tumor shown in Fig. 463 recurrent after a nine-year interval. (×200.) (W.U. neg. 49-4000.)

Malignant Change in Mixed Tumors.—Malignant change in a mixed tumor is to a great extent influenced by the liberality of the pathologist's diagnosis. Recurrent mixed tumors are not usually malignant mixed tumors. They represent only persistence of a previously inadequately excised mixed tumor. We believe that this is the usual cause rather than multiple foci of origin. The only evidence of multiple foci of origin that we know of is in some unpublished observations of State who performed total parotidectomy with preservation of the facial nerve in 50 consecutive parotid salivary gland tumors. In this group of 50 mixed tumors he found 2 which he thought showed multiple foci of origin. Usually the microscopic pattern of the recurrent or persistent mixed tumor exactly mimics the previous excision (Figs. 463 and 464). Such recurrences may take up to 50 years to develop but more often they recur repeatedly over a period of several decades. The highest percentage of local recrudescences appears in the first 18 months following the primary operation. There is no doubt that infrequently malignant transformation may take place in a mixed tumor (less than 5 per cent)

(Rawson) It is true that the proof of malignant change may be difficult If a patient has a clinical history of a long persisting tumor which suddenly begins to grow and microscopic examination shows an obvious malignant tumor, if there is no pre existing evidence of a benign mixed tumor it cannot be said that it arose in a mixed tumor purely on the basis of the clinical story It is necessary to have microscopic evidence of previously existing mixed tumor or to have malignant tumor and benign mixed tumor in the neoplasm Such cases in our experience, are few Buxton found only three such proved cases in his large series. Clinical evidences of malignant change in a mixed tumor are increases of growth pain facial paralysis and other signs which accompany a primary malignant tumor of salivary gland origin. Microscopic evidence of malignant change includes increasing cellularity, with prominence of the nuclei and nucleoli, many mitotic figures some of them abnormal and areas of necrosis in the tumor Nerve sheath invasion and local and distant metastases indicate obvious cancer In our experience, any mixed tumor which becomes malignant is usually one of extremely long duration which has been poorly treated by surgery and/or irradiation (Buxton, Rawson)

Malignant Tumors

Malignant tumors of the parotid salivary gland are much fewer in number than benign mixed tumors. The relative proportion between benign and malignant is difficult to estimate, in the Mayo Clinic series it was about 3.5 to 1 (Kirklin)

CLASSIFICATION OF TUMORS OF THE SALIVARY GLAND

Benign Tumors

- Hemangioma
- Lipoma and Neurilemoma
- Oxyphil Adenoma (Oncocytoma)
- Papillary Cystadenoma Lymphomatosum (Warthin's Tumor)

Mixed Tumors

Malignant Tumors

- Adenocarcinoma (Cylindromatous Type)
- Mucoepidermoid Carcinoma
- Papillary Adenocarcinoma
- Epidermoid Carcinoma
- Carcinoma—Hypernephroid Type (Acinic Cell Adenocarcinoma)
- Carcinoma—Unclassified
- Malignant Lymphoma
- Metastatic Carcinoma

The only reason for making such a classification of salivary gland tumors is that individual tumors may behave differently from the clinical standpoint or respond differently to irradiation therapy These malignant neoplasms may show areas of infiltration, have poorly defined margins, and have areas of necrosis (Fig 465) The adenocarcinoma and mucoepidermoid carcinoma may contain zones of apparent mucoid formation Other neoplasms may show extremely cellular areas, and zones of necrosis are common The differences between benign and malignant salivary gland tumors are summarized in Table 21

TABLE 21 DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT SALIVARY GLAND TUMORS*

	BENIGN	MALIGNANT
Clinical history		
Rate of growth	Slow (years)	Rapid (months)
Sex	More frequent in females	No essential difference
Age	Peak before 40 years	Peak about 50 years
Pain	Usually absent	Invariably present
Physical examination		
Fixation	Freely movable	Often fixed to skin deep structures, bone
Facial nerve paralysis (parotid tumors)	Unusual	Common (about 55 per cent)
Consistency	Firm, cystic nodular	May be stony hard
Growth pathology	Well-circumscribed capsule often shows cartilage	No capsule invasion of bone and contiguous tissue
Metastases	Never	Rather frequent (lymph nodes, lungs bone)

*From Ackerman L. V and del Regato, J A.: Cancer St. Louis 1947 The C. V Mosby Co p 639



Fig 465 —Clinical photograph of a highly malignant salivary gland tumor Note infiltration of the tumor with secondary ulceration (EFSCH 48-10058.)

Adenocarcinoma (Cylindroma) —The microscopic pattern of this specific type of tumor has certain well-defined characteristics This adenocarcinoma (cylindroma type) forms well-defined glands which then produce large amounts of epithelial mucin (Fig 466) The microscopic pattern of these tumors is treacherous for they appear rather benign However in our experience, these neoplasms, if inadequately treated eventually cause the death of the patient. Extreme

microscopic variations may occur in which the glands of the tumor disappear, and only small nests of highly infiltrative tumor cells are seen These cells may on mucicarmine stains show small amounts of epithelial mucin Such tumors stubbornly recur and show high proclivity for involvement of nerve sheaths (Quattlebaum McDonald) (Fig 467) These tumors frequently metastasize to the lungs without clinical evidence until seen on roentgenographic examination If one of these tumors is diagnosed a radical surgical approach should be used no matter how benign it appears under the microscope Inoperable recurrences show prominent temporary response to irradiation therapy (Baclesse) This tumor often is incorrectly reported as a malignant mixed tumor

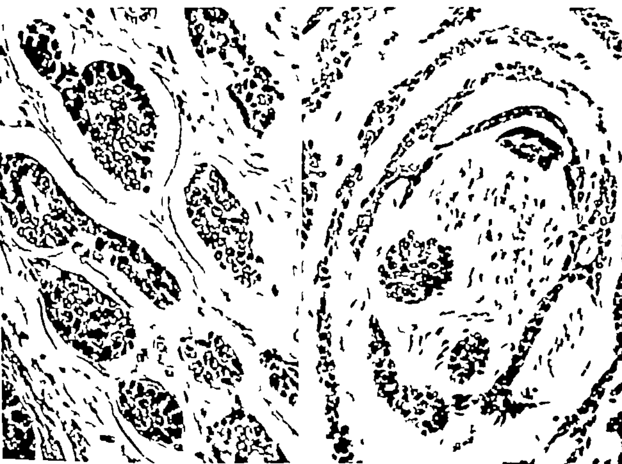


Fig 466.—Photomicrograph of an adenocarcinoma (cylindromatous type) of the salivary gland. Note well-differentiated pattern. This tumor metastasized to the lung (×360) (W U neg 51 1954)

Fig. 467 —Photomicrograph of nerve sheath invasion in an adenocarcinoma (cylindromatous type) of the salivary gland (×320) (EFSCH 43 1351)

Mucoepidermoid Carcinoma.—The mucoepidermoid tumor of the salivary gland has been well described by Foote. However the microscopic appearance should be clearly defined. It consists of two elements mucin producing cells plus areas of squamous change within the ducts (Fig 468) The tumor shows areas of mucin formation and keratin formation. When the keratin escapes into the interstitial tissue it causes an inflammatory reaction The malignant nature of



Fig 468 —Photomicrograph of a well-differentiated mucoepidermoid carcinoma. Well-differentiated squamous cells together with mucin producing cells are present. (High power) (Courtesy Dr A. P Stout New York.)



Fig 469 —Photomicrograph of a well-differentiated papillary adenocarcinoma. (×250.) (W U neg 50-2842)

this tumor has been underestimated We have seen some instances where the tumor appeared rather benign, yet in time, this tumor recurred invaded and metastasized We therefore feel that a fairly radical approach is indicated. However in most instances there is good correlation between the microscopic pattern of the tumor and its eventual behavior (Woolner)

Papillary Adenocarcinoma —The papillary adenocarcinoma is an extremely rare neoplasm In our experience it grows large, has well-defined papillary structures may form mucin and in the large tumors, hemorrhage and necrosis are common (Fig 469)

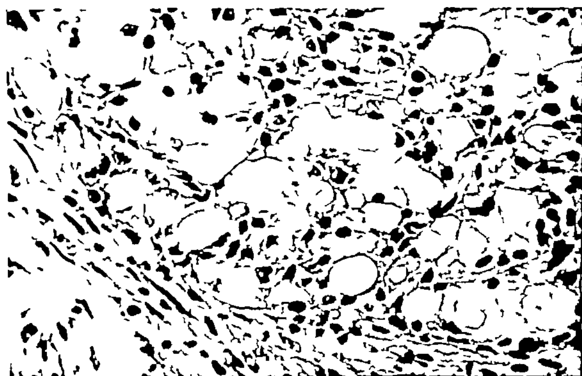


Fig 470 —Photomicrograph of a carcinoma of the hypernephroid type Note resemblance of the cells to the usual carcinoma of the kidney (×400) (W U neg 51 152)

Epidermoid Carcinoma —The epidermoid carcinoma undoubtedly arises from squamous metaplasia of the lining epithelium of the ducts These epidermoid carcinomas eventually infiltrate surrounding structures and grow rather rapidly Overgrowth by *the squamous component* may be the origin of *some of these* tumors Mucin stains may at times substantiate this supposition. Irradiation therapy may prove helpful. Many supposedly primary epidermoid carcinomas in reality represent metastases to nodes within the parotid salivary gland These metastases arise frequently from an epidermoid carcinoma of the skin.

Carcinoma—Acinic Cell Adenocarcinoma (Hypernephroid Type) —There is a rare slowly growing carcinoma which microscopically closely resembles a renal cell carcinoma (Atlas du Cancer) This tumor has a rather foamy cytoplasm (Fig 470) but does not contain cytoplasmic fat or epithelial mucin Glycogen is present in small amounts. It often is incorrectly diagnosed as metastatic carcinoma from the kidney and has even been described as an adenoma. Radical surgical therapy is indicated Neck dissection does not appear indicated (Godwin)

Carcinoma—Unclassified.—There remain a few highly undifferentiated carcinomas in which growth and infiltration are rapid. Usually, their malignant nature is evident clinically. In a few instances, however, we have seen highly undifferentiated carcinomas of the salivary gland which have grown rather slowly

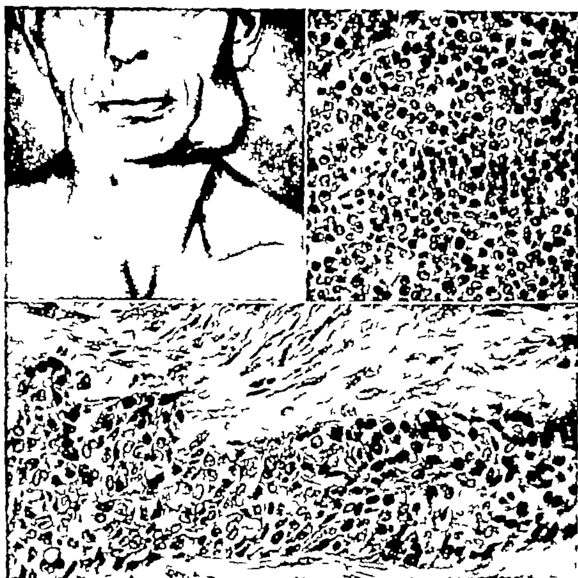


Fig. 471.—Clinical photograph of a patient with tumor of the parotid salivary gland. There is no evidence of facial nerve paralysis. Tumor had been growing rather rapidly and it was not known whether it was benign or malignant. (Courtesy Dr. Franz Leidler, Veterans Hospital, Jefferson Barracks, Mo.)

Fig. 472.—Photomicrograph of aspiration biopsy shows highly undifferentiated malignant neoplasm. (×200.) (W.U. neg. 50-1421.)

Fig. 473.—Photomicrograph of the tumor removed by radical resection demonstrating its origin from one of the parotid ducts. (×200.) (W.U. neg. 50-1420.)

and produced a clinical picture suggesting a mixed tumor. This is the type of tumor which in the past was diagnosed as a sarcoma microscopically. Multiple sections often can prove the origin of this tumor from the epithelium of the ducts of the salivary gland (Figs. 471-473).

Malignant Lymphoma.—Malignant lymphoma occurs primarily in the parotid salivary gland or the submaxillary gland but can arise in any of the salivary glands. These lesions appear to grow slowly. The microscopic differentiation of lymphoid hyperplasia from true lymphoma may be extremely difficult. In this respect these lesions resemble some of the lymphomas around the eye and its adnexa. Lymphomas can involve the salivary gland as a part of a disseminated process. We have not seen Hodgkin's disease primarily involving the salivary gland.

Metastatic Carcinoma.—Metastatic cancer in the region of the parotid salivary gland can occur. It is particularly confusing there because of lymphoid tissue within the substance of the parotid gland. With growth of the tumor a primary malignant neoplasm of the salivary gland can be exactly mimicked. In the parotid gland the two tumors which most commonly metastasize to it are epidermoid carcinoma of the skin and malignant melanoma.

SPECIAL CONSIDERATIONS BECAUSE OF LOCATION

Tumors of the *parotid salivary gland* are of the highest significance and of great concern because of the intimate relation of the parotid salivary gland to the facial nerve. The facial nerve may have various modifications in its distribution (McCormack). Bailey has a concept of its anatomy which is different from some of the American authors. He believes that the parotid gland is a bilobed structure with a broad superficial lobe and a smaller deep lobe with the facial nerve running between the two lobes. Variations of this anatomy occur. He feels that if a tumor involves the superior portion of the parotid, this can be dissected free and the facial nerve saved. He also has performed complete removal of the parotid salivary gland with preservation of the facial nerve. In the malignant tumors of the salivary gland there should be no hesitation in sacrificing the facial nerve with later plastic repair to the eyelid.

In the *submaxillary gland* area the most common tumor is a metastatic carcinoma within the submaxillary lymph nodes. The primary tumor usually arises within the oral cavity. If however there is a definite primary neoplasm of the submaxillary gland it may be excised widely without fear of damage to nerves or other vital structures. The recurrence rate of submaxillary gland tumors is relatively high because of the gland's close relation to the mandible, which is the critical point in adequate removal of this neoplasm. It must be remembered that a relatively high percentage of the tumors of the submaxillary gland are malignant as compared to the tumors of the parotid gland. In Stout's series one out of three parotid gland tumors was malignant as compared to about an equal incidence of benign and malignant tumors of the submaxillary gland (Table 22). In the *lip* salivary gland tumors usually occur in the upper lip because the mucous glands are most prominent there. They usually present as a well-defined rubbery small tumor without ulceration. The diagnosis can often be made clinically. Careful excision is all that is necessary and usually such neoplasms are benign. Within the *oral cavity* mixed tumors can occur in any location including gum, buccal mucosa, hard palate, soft palate, tonsillar area and even tongue (Brunschwig). They are

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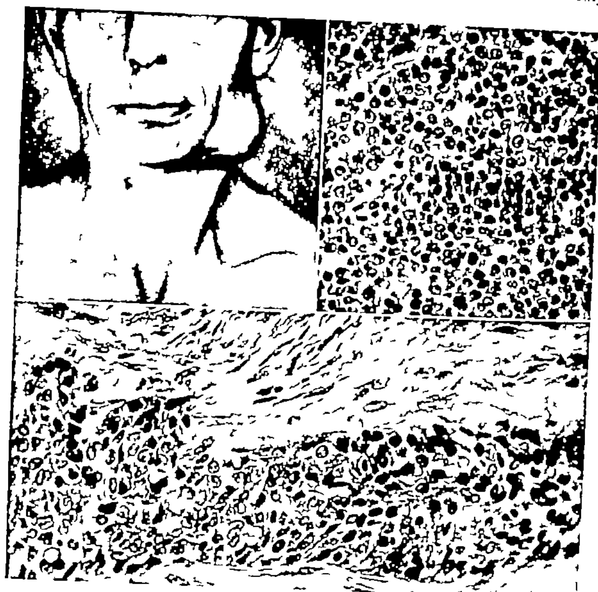


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TABLE 22 573 TUMORS OF THE MAJOR SALIVARY GLANDS RECORDED IN THE SURGICAL PATHOLOGY LABORATORY WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS

Parotid Gland					
Mixed Tumors	Primary benign	254			
	Recurrent benign (persistent)	49			
	Malignant	19			
			322		
Carcinoma	Epidermoid	30			
	Acinic cell adenocarcinoma	2			
	Undifferentiated	25			
	Mucoepidermoid	25			
			82		
Adenocarcinoma	Simple	12			
	Papillary	3			
	Cylindromatous	20			
			35		
Papillary cystadenoma lymphomatosum (Warthin's tumor)	Unilateral	30			
	Bilateral	4			
			34		
Oxyphil adenoma		4	4		
Lipoma		1	1		
				478	
Submandibular					
Mixed Tumors	Primary benign	25			
	Recurrent benign (persistent)	5			
	Malignant	1			
			31		
Carcinoma	Epidermoid	4			
	Undifferentiated	6			
	Mucoepidermoid	2			
			12		
Adenocarcinoma	Simple	1			
	Cylindromatous	11			
			12		
Papillary cystadenoma lymphomatosum (Warthin's tumor)		1	1		
				56	
Other Locations					
Mixed	Primary benign	17			
	Malignant	2			
			19		
Carcinoma	Undifferentiated	2			
	Acinic cell adenocarcinoma	1			
	Mucoepidermoid	4			
			7		
Adenocarcinoma	Simple	1			
	Cylindromatous	12			
			13		
				39	
Total					573

distributed in incidence almost proportional to the amount of mucous gland tissue. They are therefore most common in the hard palate (Hobaek) These tumors, for the most part form rather firm, rubbery nonulcerated masses. The diagnosis

may not be suspected, and at times the incisional biopsy may be too superficial to reveal the tumor. Incisional biopsy, however, can make the diagnosis, and once the diagnosis is assured the tumor should be excised if possible, with a normal margin of tissue. All types of salivary gland tumor can occur in the oral cavity (Hoback). Tumors of *lacrimal gland* origin are rare and grow in the outer half of the superior orbital brim. With increased growth they cause distortion, downward displacement, and protrusion of the eye. These tumors appear to be encapsulated and are usually enucleated. Microscopically they can reveal any type of salivary gland tumor. There is one important clinical distinction: these neoplasms, whether mixed tumors or carcinomas, are almost always badly treated. Recurrence invariably appears because of enucleation and this recurrence may be excised. In time there is bone involvement and deep extension into the orbit (Figs. 474-476). Death eventually follows. Unfortunately there are few series with long enough follow up to prove how important it is to do a primary radical operation. Sanders reported 12 patients, 11 of whom were treated surgically. All 11 had recurrences ranging up to thirteen years after the first excision. Of these 11, 6 have already died (Sanders, Forrest).

In the *trachea* and *bronchus* there are rare salivary gland tumors which resemble mixed tumors. We have seen only one such neoplasm that was in the trachea. However, in the trachea and in the bronchus we also see adenocarcinomas of the cylindromatous type. These tumors have the same slow clinical course as tumors in other salivary glands but if inadequately treated may recur and cause death. They should be separated from the usual type of so-called bronchial adenoma. This is well illustrated by both Holley and Belsey.

BIOPSY IN TUMORS OF SALIVARY GLAND ORIGIN

We have already commented on the necessity of biopsy for tumors of salivary gland origin within the oral cavity, indicating the need of a small deep incisional biopsy. There is usually little necessity for biopsy of submaxillary gland tumors. The greatest difficulty is in the region of the parotid salivary gland where it would be helpful to know the exact pathology before embarking upon surgery. It is obvious that biopsy would not be required for the obviously malignant or obviously benign tumors. It is only in the borderline group that it is of such great importance. Needle biopsy of salivary gland tumors for accurate diagnosis prior to contemplated surgery is difficult. The microscopic diagnosis of squamous carcinoma, undifferentiated tumors, and mixed tumors is not difficult. However, on several occasions we have not been able to make the differential diagnosis between an adenoid cystic carcinoma and a benign neoplasm. Furthermore, we have demonstrated implantation along the needle tract. Therefore, we have found the use of this diagnostic procedure limited. In several instances careful incisional biopsy has been done. If the tumor proved to be malignant, then this area of biopsy could be encompassed by the subsequent surgical procedure. We have also not hesitated to do frozen section in some of these debatable salivary gland tumors. In some instances we have been able to make a definitive diagnosis for a malignant or benign salivary gland tumor. In the malignant group, particularly of the cylindromatous

type if this diagnosis is made it is practically mandatory to combine the surgical procedure with a radical neck dissection In one instance fixation to the skin was present and frozen section revealed a benign papillary cystadenoma rather than carcinoma. It is true that the interpretation of frozen section of salivary gland tumors is difficult and requires considerable experience and judgment.



Fig 474 —Clinical photograph of patient with recurrent mixed tumor of the lacrimal gland. (W U neg. 51-6191)

Fig 475 —Photomicrograph of the tumor shown in Fig 474 at the time of original incomplete removal in 1941 It appears to be a benign mixed tumor (400) (W U neg 52 534)

Fig 476 —Photomicrograph of the recurrent tumor in 1952. There were areas which showed evidence of pre-existing mixed tumor and this area shows evidence of carcinoma with atypical mitotic figures and prominent cellularity (×600) (W U neg 52 535)

CLINICOPATHOLOGIC CORRELATION

In tumors of salivary gland origin the benign tumors require little comment. The most important remarks relate to mixed tumors and obvious carcinomas. Recurrence in mixed tumors is almost entirely dependent on the adequacy of the primary operation. Inadequate procedures such as enucleation of the tumor and contamination of the operative field will bring the recurrence rate to a high level (Fig 477). Thus recurrent rate is more dependent on the surgery than on the microscopic pattern of the tumor. Recurrences may occur over an exceedingly long time period and all patients with mixed tumors must be followed for life.

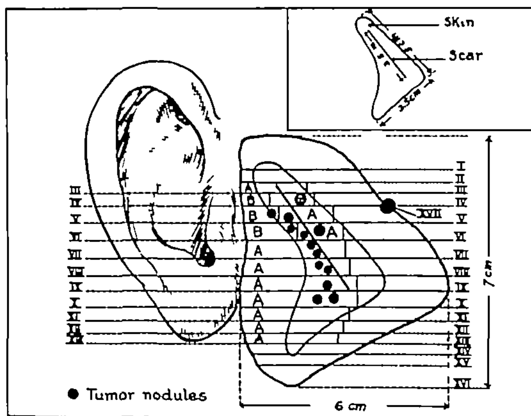


Fig. 477.—Diagrammatic sketch of the distribution of recurrent tumor as demonstrated in the careful histologic study of the re-excision of a persistent mixed tumor which at the time of the first operation had apparently been enucleated. (Courtesy Dr Franz Leidler Veterans Hospital, Jefferson Barracks Mo.)

Few patients with mixed tumors ever die of this disease. In 296 traced patients with primary mixed tumors followed at the Mayo Clinic only four died of tumor (Kirklin). In malignant salivary gland tumors we do not have exact information as to their prognosis on the basis of the type, but it is obvious that in the operable cases radical procedures must be done with sacrifice of facial nerve whenever there is doubt about it. Consideration of primary irradiation therapy should probably be given to an obviously inoperable tumor rather than inadequate resection followed by postoperative irradiation.

Rare Lesions.—We have seen several rare lesions which have been mistaken clinically for a neoplasm. These include a single instance of *cat scratch disease* involving the lymph node within the parotid two instances of *epidermal inclusion*

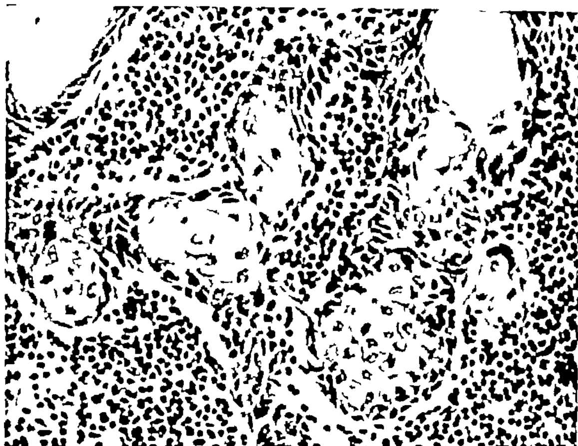


Fig 478 —Photomicrograph of sebaceous-gland hyperplasia associated with lymphocytic infiltration within the parotid gland. (×440) (W U neg. 57 98A.)

cysts in the region of the parotid which were thought to be carcinoma, and finally an area of deep induration caused by a *healed abscess* that had been drained 20 years previously *Sebaceous glands* are rarely included in the region of the parotid and have been known to cause a poorly delimited mass which can be mistaken grossly and microscopically for cancer (Fig 478)

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Chapter 11

LIVER

ASPIRATION AND INCISIONAL BIOPSY

Aspiration biopsy of the liver is a useful diagnostic procedure its use obviate a major operation or resolve an obscure medical diagnostic problem. Silverman needle has proved effective because it removes a block of tissue f which paraffin sections can be made. Another needle recommended by Pop called the Terry needle produces less distortion of the biopsy At the the biopsy is studied grossly we recommend that a small fragment be saved frozen section and fat stain Rare deaths have resulted from this procedure F found 14 cases in the literature. Twelve occurred when the intercostal appr was used he therefore recommends that the needle be inserted through the terior abdominal wall at the midclavicular line just below the right costal bo unless there is a palpable nodule in the liver The risk is slight and the re well justified Gillman performed 500 biopsies without complication Ne biopsy is contraindicated in patients with bleeding tendencies and in those long standing extrahepatic biliary obstruction because of the possible ruptu dilated bile ducts close to the capsular surface.

We have found aspiration biopsy diagnostically definitive in the presenc primary hepatic neoplasms, metastatic carcinoma, and melanocarcinoma 479) There are medical diagnostic problems where aspiration biopsy is dec Diagnoses of amyloid disease of the liver (Fig 480) tuberculosis other gr lomatous processes and hemochromatosis have been made. The greatest diffi

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lies in differentiating the various types of cirrhosis and conditions such as infectious hepatitis (*Fig* 481)

The pathologist should not attempt diagnosis by needle biopsy without having all clinical and laboratory data available He must know whether or not these

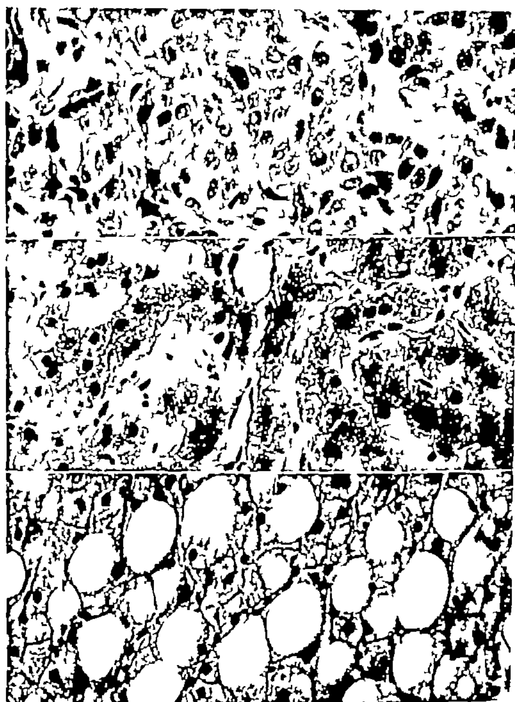


Fig 479.—Photomicrograph of aspiration biopsy demonstrating metastatic carcinoma within the liver Primary source uncertain (×400) (W U neg 50-2052)

Fig 480.—Photomicrograph of aspiration biopsy This demonstrates amyloid disease of the liver which was unsuspected before the biopsy *The amyloid is present between the liver cords.* (×400) (W U neg 50-2054)

Fig 481.—Photomicrograph of aspiration biopsy demonstrating extreme fatty metamorphosis in a patient who was a chronic alcoholic. (×400) (W U neg 50-2053)

findings indicate bile duct obstruction or hepatocellular damage Such information is required because *the cellular findings in various liver diseases vary with the stage* of the process and actually shade from one disease process to another Tables 23 and 24 summarize the characteristic histologic and laboratory findings in the different types of hepatitis and obstructive jaundice. It should be realized that the findings listed actually overlap considerably

TABLE 23 BILE STASIS (JAUNDICE)*

	DUE TO EXTRAHEPATIC OBSTRUCTION		DUE TO INTRAHEPATIC OBSTRUCTION	
Hepatic Cells	*Early*	*Late*	*Early*	*Late*
Degeneration	Present	Severe	Minimal	Present
Necrosis	Present	May be severe	Minimal	May be present
"Bile lakes"	Usually absent	Present	Absent	May be present
"Bile infarcts"	Often present	Present and large	Absent	Usually absent
"Bile laden Kupffer cells"	Present	Present	Present	Present
Biliary System	*Early*	*Late*	*Early*	*Late*
Canalicular dilatation with bile plugs	Present	Present	Present	Present
Intralobular duct dilatation with bile plugs	Present	Present	Present	Present
Proliferation of ductules	Absent	Present	Absent	Present
Inflammation about ductules	Absent	May be present	May be present	Present and *often severe*
Bile duct dilatation with bile plugs	May be present	Present	Absent	Absent
Inflammation about ducts	Edema only	Present	Absent	Absent
END STAGE OF OBSTRUCTIVE PROCESS	BILIARY CIRRHOSIS		CHOLANGIOLITIC CIRRHOSIS	

*Table compiled by Dr Walter Bauer Department of Surgical Pathology Washington University School of Medicine

Successful differentiation of the various types of cirrhotic and fibrotic lesions of the liver can often be accomplished by the study of needle biopsies of the liver Nutritional cirrhosis nearly always presents a characteristic histologic picture with an adequate biopsy specimen by virtue of the diffuse nature of the disease throughout the liver The distinctive pattern of fibrosis, the presence of rather uniform regenerative nodules without central veins, and the vestiges of fatty cysts in the stromal component provide features of diagnostic importance usually found in the majority of biopsies. The diffuse fibrosis associated with long standing congestive heart failure Thorotrast deposition in the liver and hemochromatosis also present easily recognized microscopic patterns. Difficulty sometimes arises in the interpretation of biopsies from the livers of postnecrotic (posthepatitic) cirrhosis due to the minimal changes or the spotty distribution of the fibrotic areas The pattern of parenchymal collapse may not be seen on random biopsy or the changes may be so minimal as to be only suggestive of the diagnosis Furthermore biopsies taken from advanced stages of cirrhosis may present a confusing pattern that does not permit an etiologic diagnosis even at the time of autopsy when examination of the entire liver is possible.

The surgeon who plans biopsy of the liver should *perform the formal incisional biopsy* immediately upon entering the peritoneal cavity If he delays biopsy until the end of an operative procedure inflammatory infiltration and distortion of the parenchyma beneath the liver capsule and even infarction caused by abdominal

TABLE 24 TYPICAL EARLY AND LATE MICROSCOPIC FINDINGS IN LESIONS OF THE LIVER PRODUCING JAUNDICE*

CAUSES	TYPICAL MICROSCOPIC FINDINGS (NEEDLE BIOPSY)		LABORATORY FINDINGS
	Early (or Initial Attack)	*Late (or Relapsing)*	
Hepatitis (Diffuse or irregular distribution) Infectious or serum hepatitis)	Portal mononuclear infiltrate (lymphocytes, plasma cells, eosinophils)	Some degrees of the early changes	All liver function tests abnormal
	Absence of stainable neutral fats (Sudan III stain)	Parenchymal collapse	Abnormal thymol turbidity and cephalin flocculation test
	Diffuse parenchymal disorganization and degeneration	Condensation of stroma (reticulin stain)	Decreased serum albumin and prothrombin time
	Balloon degeneration	Regenerative nodules (irregular)	Slight elevation of alkaline phosphatase (except in children)
	Polymorphism and multinucleate cells	Presence of ceroid pigment (fat-stain paraffin section)	Elevated total serum bilirubin, serum transaminase serum globulin
	Individual cell degeneration (acidophilic bodies)	Postnecrotic cirrhosis	
	Pseudotubule and pseudoacinus formation		
	Early	*Late*	
Hepatitis (Cholangiolitic distribution) (Cholangiolitic hepatitis)	Severe centrilobular canalicular and ductal biliary stasis	Some degree of early changes, particularly periductular mononuclear infiltrate	Elevated total serum bilirubin and total cholesterol slightly elevated alkaline phosphatase
	Periductular mononuclear infiltrate	Ductular proliferation	Normal flocculation tests and serum proteins
	Only occasional and often rare parenchymal necrosis and acidophilic bodies	Periductular fibrosis (connective tissue stain) (stellate portal areas)	Slight to marked elevated serum transaminase
		Cholangiolitic cirrhosis	

	Early (up to 3 to 6 months)	*Late (after 3 to 6 months)*	
Obstructive Jaundice (Biliary duct obstruction stone, cancer metastatic disease)	Centrilobular canalicular biliary stasis	Early changes	Elevated serum sodium bilirubinate alkaline phosphatase total cholesterol
	Periductal inflammation (edema few neutrophils)	Often severe periductal inflammation (many neutrophils)	Normal flocculation tests and proteins
	"Feathery degeneration" hepatic cells	Bile duct and ductular dilatation and bile stasis	
	Bile infarcts"	Bile infarcts and "bile lakes	
		Periportal connective tissue proliferation	
		Ductular proliferation	
		Biliary cirrhosis	
	Early	*Late*	
Obstructive Jaundice (Ductular obstruction allergic cholangiolitis, arsenic, methyl testosterone chlorpromazine)	Centrilobular canalicular biliary stasis	Early changes often severe periductular inflammation	Elevated total serum bilirubin and alkaline phosphatase and total cholesterol
	Ductular dilatation with bile stasis	Periductular fibrosis	Other liver function tests normal
	Periductular inflammation (eosinophils) extending into liver lobule	Cholangiolitic cirrhosis	
	Minimal involvement of lobular bile ducts		

Table compiled by Dr Walter Bauer Department of Surgical Pathology Washington University School of Medicine

retractors may be present. Because of the more marked fibrotic changes in the subcapsular area, the surgeon should perform not only incisional biopsy but also a deeper parenchymal needle biopsy in all diagnostically difficult cases.

Post demonstrated that the histologic appearance of the liver frequently is poorly correlated with the clinical state of the patient and laboratory tests for liver function In fact, it is often difficult, if not impossible to correlate the pathologic findings with various liver function tests and clinical state of the patient. He did find, as did Popper that necrosis correlates with advanced liver disease. There may be prominent structural derangement of the liver associated with clinical improvement There is much better correlation between the clinical state and the hepatic functional tests As Popper emphasized, the altered pathologic changes in the liver persist long after there has been pronounced clinical and laboratory improvement. Serial needle biopsies are helpful in following the course and the effect of treatment in various forms of hepatitis and nutritional cirrhosis.

ABSCESS

Metastatic foci may occur in the liver during systemic inflammatory processes. The most important inflammatory complication from the surgical standpoint is pylephlebitis secondary to periappendiceal abscess Infected thrombi in the radicals of the portal system travel to the liver resulting in multiple abscesses in the liver parenchyma The etiology of this condition often is not recognized because it is overshadowed by the other clinical symptoms The patients are extremely ill with spiking fever Pylephlebitis is very rare today Abscesses of the liver such as amebic, are relatively uncommon in this country They occur secondarily to lesions of the gastrointestinal tract and are recognized only after tissue study amebae may be found in fresh material from the abscess wall

ECHINOCOCCUS CYSTS

Echinococcus disease of the liver is rare in the United States but common in Iceland Australia, Turkey South America, and New Zealand Hydatid disease is caused by the larval or cystic stage of the dog tapeworm *(Taenia echinococcus)* Its definitive hosts are dogs wolves cats and other carnivora. The intermediate or cystic stage is present in sheep hogs and cows, but man or other mammals can become infected The most common site of echinococcus cysts is in the liver (60 to 70 per cent of instances) and lung The pulmonary cysts may become calcified and encapsulated after which the skin test is of little value and eosinophilia may be absent or not over 5 per cent (Hudson) The diagnosis can be made by macerating a small piece of germinal layer in saline and then finding the scolices. The histologic examination of a section from the cyst wall often is diagnostic.

CYSTS

Cysts of the liver occur most frequently in patients between 40 and 60 years of age and are more common in women They are extremely rare in children (Sanes) Congenital cystic disease of the liver also is relatively rare Moschcowitz collected 85 cases, 75 of which were associated with cystic lesions or other dis

orders of the kidney By contrast only 19 per cent of patients with congenital cystic disease of the kidney have associated lesions of the liver There may also be cysts in other organs such as the pancreas spleen or lung

Cystic disease of the liver may be related to local obstruction of biliary ducts resulting in retention cysts. These cysts are more common on the right side and may attain a diameter of 8 or 10 cm. They usually are intrahepatic but may be pedunculated. Grossly they have well formed fibrous tissue walls and on section are honeycombed with numerous cavities which contain clear fluid or bile. Necrosis and calcification may occur (Montgomery) The cysts may undergo torsion and hemorrhage (Ackman) The intervening hepatic tissue is compressed by the cysts. The lining of the cyst is flattened bile duct epithelium Removal is the approved treatment (Maingot Claggett)

TUMORS

The following classification of tumors of the liver has been modified from Warvi

I Primary tumors of the liver without specific hepatic elements (vascular fibrous adrenal rests etc.)

II Hepatomas
- A. Liver cell adenomas
- B. Liver cell carcinomas (with or without cirrhosis)

III Cholangiomas
- A. Adenomas of intrahepatic bile ducts (solid or cystic)
- B Duct cell carcinomas

IV Cholangiohepatomas (with both liver cell and duct cell elements)

Primary Tumors of the Liver Without Specific Hepatic Elements

Benign tumors and other lesions of the liver may be mistaken at operation for metastatic carcinoma. Small fibrous scars and healed tubercles resulting from ancient postprimary hematogenous dissemination are commonly mistaken for tumor More rarely a tuberculous lesion may form nodular masses in the liver particularly in the Negro Even more rarely a gumma forms in a nodular mass and is mistaken grossly for a malignant neoplasm. Such lesions have been resected because they were thought to be carcinoma (Pickrell) The most common of these nonmalignant lesions are the *lymphangioma* and the small cavernous *hemangioma* both of which may have an intermingling of elements and probably could be designated as hamartomas. They usually project slightly above the cut surface and are fairly firm. On section their benign nature is apparent. Hemangiomas occasionally grow large enough to form a clinically apparent mass They sometimes are pedunculated (Fig 482) Shumacker reviewed the literature on large hemangiomas and found 56 cases. He emphasized that bleeding from these neoplasms may be excessive Spontaneous rupture occasionally occurs (Hendrick) Microscopically these benign tumors have no special features

Hepatomas

The term hepatoma should be reserved for those neoplasms which arise from liver cells and mimic such cells. The true adenoma of the liver is a rare entity

its diagnosis rests not only on the gross and microscopic findings but on the clinical follow up. These lesions shade imperceptibly into carcinoma. Grossly such a tumor has a well-defined capsule and a different color than the surrounding liver. The destruction and regeneration of liver parenchyma precedes the formation of liver cancer. Histologically, the diagnosis of hepatic cancer may be difficult because the regenerating changes may shade into frank cancer. Microscopically the adenoma is made up of a solid mass of well-differentiated liver cells with abundant eosinophilic granular cytoplasm. There are no portal triads or central veins. Multiple sections must be studied to rule out malignant change. There should be no evidence of blood vessel invasion. Hepatomas do not connect with the duct system of the liver.



Fig 482.—Gross photograph of hemangioma of the liver occurring in a child. It was successfully removed. (W U neg 54-5739)

Liver Cell Carcinoma

The liver cell carcinomas may be divided broadly into those associated with cirrhosis and those not. This division has practical significance because the carcinoma associated with cirrhosis usually is widespread in the liver making resection impossible. The gross examination may show a single large mass multiple masses with cirrhosis or multiple masses without cirrhosis (Fig 483). Microscopically primary liver carcinoma shows great variation in the size and shape of cells tumor giant cells and bizarre mitotic figures (Fig 484). The individual tumor cells in a carcinoma have much less cytoplasm than in an adenoma and their nuclei and nucleoli are more prominent. With increasing anaplasia the staining reaction of

the cytoplasm becomes basophilic. Tumor cells often line vascular sinuses; they may contain bile pigment. Frequently there is blood vessel invasion by the tumor. Carcinoma associated with cirrhosis probably is multicentric in origin.



Fig. 483.—Gross photograph of a pedunculated hepatoma in an adult. This tumor was surgically excised. The patient remains well after more than five years. (W.U. neg. 50-3199.)

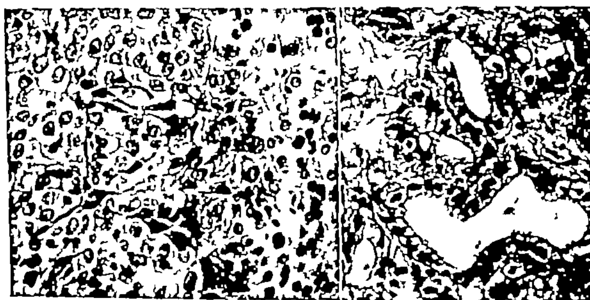


Fig. 484.—Photomicrograph of a primary liver cell carcinoma. Note resemblance of tumor cells to liver cells without normal architectural pattern. (×400.) (W.U. neg. 50-843.)

Fig. 485.—Photomicrograph of a primary malignant tumor of the liver of the cholangioma type. Note formation of glands and resemblance to bile duct epithelium. (×400.) (W.U. neg. 50-2973.)

Cholangiomas

Adenomas arising from bile ducts (benign cholangiomas) occur rarely as either solid or tubular type tumors or more commonly as cystadenoma. Several authors have collected 100 or more cases of cystadenoma (Beattie Montgomery) Only 62 solid adenomas with detailed microscopic descriptions were found in the literature 38 of these were resected surgically (Warvi) A few cases designated as hamartomas have occurred in which an adenoma of the liver has shown both bile ducts and proliferating hepatic cells (Kay) Malignant tumors of bile ducts are less common than those of liver cells and are not so frequently associated with cirrhosis they may arise within developmental cysts (Willis) Microscopically these tumors have a bile duct pattern but seldom secrete bile (Fig 485) They contain ductlike areas lined by cuboidal or columnar cells and have abundant connective tissue stroma The delicate interepithelial capillary supporting stroma characteristic of hepatoma is absent Primary malignant tumors of the liver sometimes have cells of both biliary and liver types. Usually these mixed varieties are predominantly of the liver cell type.

Primary malignant tumors of the liver quickly permeate the liver through the venous system, spread to the lung and grow into the pulmonary arterial tree local invasion of the diaphragm can occur They also may metastasize regionally to the lymph nodes at the hilum of the liver and rarely disseminate widely through the blood stream and develop extensive bone metastases.

Clinicopathologic Correlation

Primary carcinoma of the liver is most common in older men (50 to 60 years of age) possibly because of the greater likelihood of cirrhosis in them. There have been only 75 proved cases in children up to 16 years of age (Steiner) Although hepatic cancer is relatively rare in this country it is seen sufficiently often to have clinical importance. About 50 per cent of these tumors are associated with cirrhosis and undoubtedly are causally related to it. The type of cirrhosis commonly thought to precede hepatic carcinoma has been portal cirrhosis. However Higginson has shown that the postnecrotic type cirrhosis is more commonly associated with cancer This variety of cirrhosis was found in 38 of the 50 hepatomas reported by him The only possible effective treatment of primary carcinoma of the liver is complete resection but this is possible only with single well localized lesions. In the presence of cirrhosis and in cases with metastases to the hilum there is no hope of cure.

METASTATIC NEOPLASMS INVOLVING THE LIVER

If liver metastases are found at exploration for carcinoma of the stomach pancreas or the large bowel further operation can have only palliative benefit. Unfortunately practically all malignant neoplasms grow excellently in liver parenchyma. Primary malignant tumors of the stomach, pancreas extrahepatic ducts, and gall bladder frequently involve the liver by direct extension. Metastases to the liver from cancers of the large bowel, kidney pancreas, stomach lung or breast appear with appalling frequency Sarcomas too may involve the liver Car

cinoma in the liver forms discrete masses which may locally elevate the capsule and appear as poorly defined yellow or gray masses. Central necrosis with umbilication occurs in the larger nodules. Unfortunately large metastases may be completely hidden within the parenchyma. Resection of a single metastatic lesion or resection of metastases in continuity with primary tumor (cancer of the stomach, cancer of the large bowel) may yield satisfactory palliation.

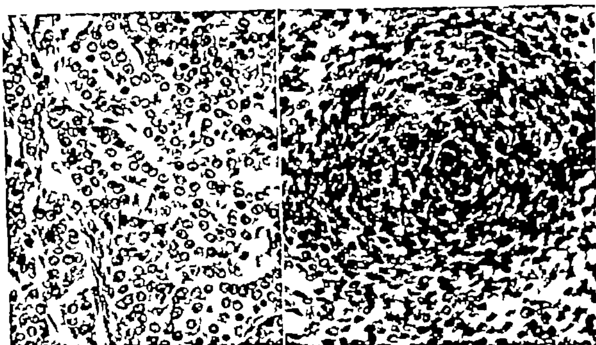


Fig 486.—Photomicrograph of closely packed tumor cells resembling liver cells in a malignant embryonal hepatoma. (×440) (W U neg 52 103)

Fig 487.—Photomicrograph of another area of the same tumor with a cellular zone similar to that often seen in a Wilms tumor (×440) (W U neg 52 102.)

OTHER MALIGNANT TUMORS

Fibrosarcomas (Shallow) and *hemangioendotheliomas* (Stout) have been reported. We have even seen several primary hepatic *leiomyosarcomas*. A rare neoplasm *malignant embryonal hepatoma* (hepatic analogue of Wilms tumor) has been described with many components including cystic areas cartilage striated muscle and bone (Roth Sheehan) (Figs 486 and 487). These tumors occur in children.

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Chapter 12

GALL BLADDER

INTRODUCTION, CONGENITAL ABNORMALITIES

Congenital abnormalities of the gall bladder are of many types They in clude duplication, absence, and anomalous positions of the gall bladder (Corcoran) There are many anomalous arrangements of the extrahepatic bile ducts and their adjoining arteries (Fig 488)

In *congenital atresia* of the bile ducts the gall bladder may be completely absent and often no extrahepatic ducts are present or these are represented by a fibrous cord without a lumen. If there are no extrahepatic ducts the liver will contain a few small bile ducts which may not even communicate with bile canaliculi No large intrahepatic ducts will be present. Obviously operative procedures are of no value under these circumstances If there is partial patency of the common duct, dilatation of ducts may occur and it may be possible to improve biliary tract drainage In adults with biliary obstruction at the porta hepatis Longmire has devised a procedure in which he cuts away a wedge shaped section of the left lobe and then anastomoses a selected large duct to the jejunum. Frozen section and gross inspection of the liver can determine the presence or absence of such ducts. Only a small percentage of infants with biliary duct atresia can be helped by anastomosis of a dilated intrahepatic or extrahepatic duct to an adjacent segment of proximal gastrointestinal tract. Only one such instance has been seen at the St. Louis Children's Hospital in the last decade Rarely dilated hepatic ducts traverse the lesser peritoneal cavity (Moore)

The concept of *Rokitansky Aschoff sinuses* and *Luschka ducts* has been defined by Halpert as follows Rokitansky Aschoff sinuses usually do not occur in the normal human gall bladder but with inflammation there is separation of the muscular wall and herniation of the mucosa which may extend to the perimuscular layer (Fig 489) True Luschka ducts are ductlike structures lined by cuboidal epithelium which are found in the outermost layer of the gall bladder wall. They have a fibrous wall and do not communicate with the lumen of the gall bladder

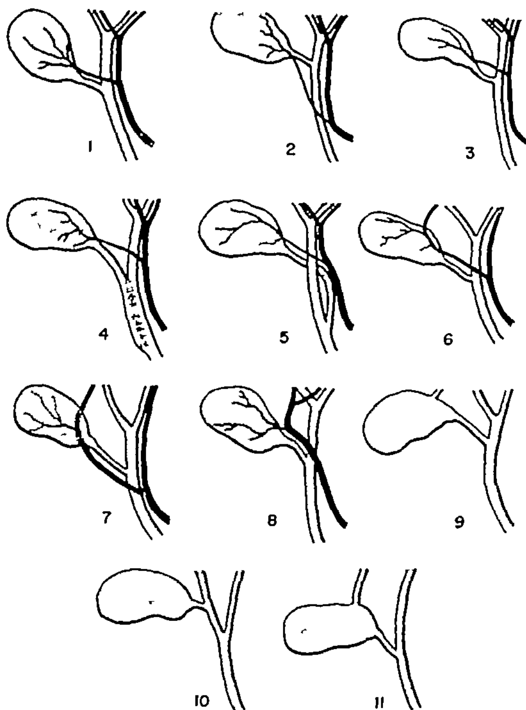


Fig 488 —Normal and anomalous arrangements of the extrahepatic bile ducts and their adjoining arteries.

1 Normal arrangement.

2 Caudad origin of cystic artery (frequent variation)

3 Placement of the cystic artery posterior to the common hepatic duct.

4 Long cystic duct attached to the common hepatic duct for some distance prior to the confluence to form the common bile duct.

5 Long cystic duct passing behind the common hepatic duct and joining it medially at a lower level.

(Legend continued on opposite page)

Robertson believes that the term Luschka's crypts and Rokitansky Aschoff sinuses should be abandoned and that they should be called diverticula of the gall bladder He found such diverticula in about one half of all gall bladders removed in patients over the age of 30 Most of them communicated with the lumen of the gall bladder but some were cut off from the gall bladder and became cysts with budlike branches (Fig 490) These crypts can contain bile, bile pigment, cholesterol crystals or true biliary calculi King has used the term cholecystitis glandularis proliferans for Rokitansky Aschoff sinuses and demonstrated a case in which these sinuses were well seen by radiographic examination.

BILIARY TRACT LITHIASIS

The pathogenesis of lithiasis is complicated by the interplay of innumerable factors. Stones in the gall bladder are common and much more frequently occur in females (ratios quoted being about four to one) About 20 per cent of them contain sufficient calcium to be radiopaque. About 50 per cent of the nonopaque stones are manifest only by nonvisualization of the gall bladder by cholecystography The others show as a negative shadow when the gall bladder concentrates the dye The incidence of stones increases with age until at 60 about one out of every four females has stones. These stones vary considerably in chemical composition. The causes for their formation in many instances are related to the distant past, and reconstruction of their pathogenesis therefore is difficult

Stones can be divided into pure mixed and combined varieties. The incidence of pure and combined stones are about equal (10 per cent) but mixed stones make up the remainder A pure stone is cholesterol calcium bilirubinate or rarely calcium carbonate. A mixed stone is made up of any combination of cholesterol calcium bilirubinate, and calcium carbonate A combined stone on the other hand usually has the shell of a mixed stone with the center of pure cholesterol or rarely calcium bilirubinate.

(Legend continued from opposite page.)

6 Normal ductal system with anomalous right hepatic artery reaching the gall-bladder wall where it gives off the cystic artery and then turns into the liver In this anomaly which is not rare, the right hepatic artery is often ligated either with the cystic duct or as a separate structure erroneously identified as the cystic artery

7 Anomalous right hepatic artery in a posterior position presenting the same dangers as in *6*

8 A very dangerous anomaly of the entire hepatic artery which follows the cystic duct to the gall bladder before turning into the liver Accidental ligation of the entire hepatic artery was almost always fatal before the development of penicillin and chlortetracycline and is still hazardous

9 Anomalous bile duct entering gall bladder through its bed in the liver Cholecystectomy in such instances is usually followed by profuse drainage of bile and is likely to result in fatal peritonitis unless external drainage is afforded

10 Anomalous insertion of cystic duct into right hepatic duct. The section of the right hepatic duct caudad to its junction with the cystic duct can easily be mistaken for the cystic duct and ligated thus shutting off the drainage of the right lobe of the liver into the intestine

11 Anomalous arrangement of the right hepatic duct in which it enters the gall bladder so that all of the bile from the right lobe of the liver must drain through the cystic duct

(From Rhoads J E. Liver Gallbladder and Bile Passages in Allen J G., Harkins H N, Moyer C. A., and Rhoads J E. Principles and Practice of Surgery Philadelphia 1957 J B Lippincott Co., p 688)



Fig 489 – Demonstration of deep pene ration of gall bladder epi ween the muscular layers (Low power) (W U 461)
Fig 490 – Blindly ending ducts branches deep in t der wall (Low power) (W U neg 48-5175)

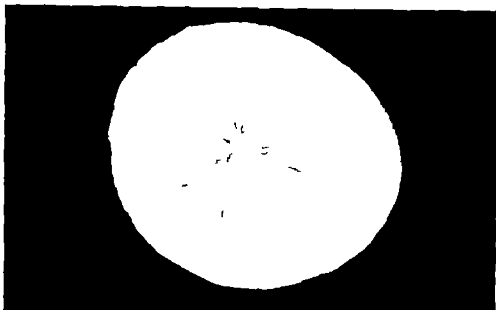
Cholesterol stones are single spheroidal coarsely nodular and translucent bluish white in color On fracture the stone shows large flat crystals (Fig 492) Cholesterol metabolism is altered in the pregnant female Usually cholesterol stones are found in multiparous women often signs and symptoms of stones develop shortly after pregnancy (Gerwig) However there is usually no correlation be tween the presence of cholesterol stones in the gall bladder and the level of choles-terol in the blood *Calcium bilirubinate stones* are small brown to jet black faceted stones measuring 2 to 5 mm In hemolytic jaundice of the congenital type where there is a long-continued increase of circulating bilirubin there is an increase of such stones and about one half of the patients with this condition show lithiasis (Giffin) Furthermore Greene found experimentally that an augmented rate of excretion of this pigment in the bile occurs by an increase in concentration rather than from increase in volume of the bile Stones of this type also form in sickle cell anemia The gall bladder containing either a cholesterol stone or pigment stones shows little or no inflammatory reaction if the cystic duct is not obstructed The finding of only pigment stones in the gall bladders of younger persons should arouse suspicion of such hemolytic diseases.

Mixed stones are the most common (80 per cent of all stones) and they con sist of various combinations of cholesterol calcium bilirubinate and calcium car bonate. Their size and number vary and several crops may be present suggest ing that the causes for their formation may operate at different time intervals (Fig 493) Combined stones are usually single and commonly have the nucleus of pure cholesterol and the shell of a mixed stone This type of large gallstone may be associated with biliary fistulas *Barrel stones* are usually two in number large and faceted on one surface and the thick walled gall bladder is closely wrapped around them (Fig 491) Gallstones are formed in the gall bladder and may escape from the gall bladder into the cystic and extrahepatic ducts. Their inde pendent formation in the extrahepatic ducts is rare. Choledocholithiasis and common-duct obstruction by stone nearly always are secondary to cholecystolithi asis. The appearance of symptoms of common-duct stones some time after chole-cystectomy for stone is nearly always caused by stones overlooked at the time of operation However the uncommon finding of multiple small intrahepatic stones suggests that they may be formed in the hepatic duct system exclusive of the gall bladder

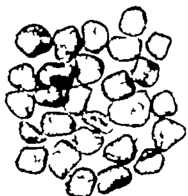
CHOLESTEROSIS

Cholesterosis of the gall bladder has a characteristic pathologic pattern and occurs in a high percentage of instances in multiparous females. Its pathogenesis is thought to be based on metabolic changes. Cholesterol is increased in the blood and bile during pregnancy but at the time of discovery of cholesterosis the blood cholesterol usually is normal. The bile salts keep cholesterol in solution. It is thought that if the bile salts fall below a certain level precipitation of cholesterol occurs However Carter has shown that about 80 per cent of noncalculus gall bladders have bile salt levels below that necessary to keep cholesterol in solution, yet no stones have been formed. Stasis is certainly a factor With cholesterosis









Figs. 491-493 —Different types of gallstones.

Fig. 491 —Two typical barrel stones, faceted on only one surface. These stones completely filled a thick walled gall bladder (W U neg 52-4431)

Fig 492.—Cross section of a single cholesterol stone showing typical crystalline structure. (*W U neg 52-4949*)

Fig 493 —Typical mixed stones with two different crops suggesting that the formation of each nest of stones occurred at different time intervals (W U neg 52-4864)

inflammation is minimal Indeed the disappearance of this condition is associated with inflammation Certainly we have not seen cholesterosis with advanced inflammatory changes in the gall bladder

Characteristically, the subserosal tissue of the gall bladder wall is slightly thickened The mucosa is prominently congested and yellow flecks of lipoid are confined to the prominences of the ridges as yellow longitudinal linear streaks (Illingworth) (Fig 494) This prominent congestion and the yellow flecks are the cause for the inelegant name of strawberry gall bladder The bile is usually concentrated clear and dark chemical analysis of it demonstrates a high concentration of cholesterol Microscopically minimal to moderate chronic inflammation is seen in the subserosal tissue Usually such inflammatory changes are observed only when there are small stones in the cystic duct (Figs 495 and 496) Foam cells are present in the tips of the villi and the fat is either in the epithelium or the stroma (Fig 497) Boyd demonstrated that this fat contains esters of cholesterol



Fig 494—Gross photograph of cholesterosis of the gall bladder Small yellow flecks are present along the mucosal ridges. (W U neg 52-4429)

ACUTE CHOLECYSTITIS

Before discussing acute cholecystitis the role of bacterial infection in acute and chronic cholecystitis should be mentioned Drennan, in a bacteriologic study of 100 gall bladders demonstrated bacteria in only 19 Feinblatt emphasized that bacterial peritonitis as a complication of acute cholecystitis is rare Furthermore if a gall bladder perforates which is infrequent, the peritoneal reaction results from the bile salts rather than from bacterial infection. Free perforation into the peritoneal cavity is a relatively rare occurrence in our institution Our surgeons promptly explore patients suspected of acute cholecystitis and frequently remove

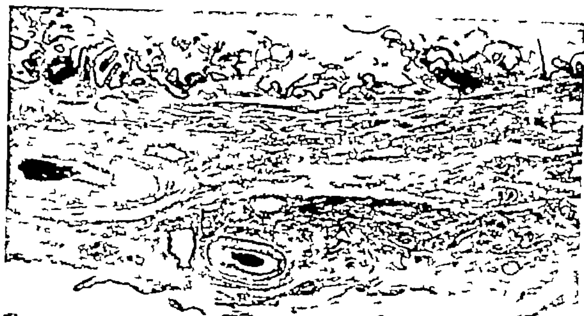


Fig 495—Photomicrograph of minimal chronic inflammatory changes in a gall bladder with cholesterosis and a small stone in the cyst c duct. Note that the thickening is in the subserosal area. (Low power) (W U neg 52-4491)

Fig 496. Photomicrograph of advanced chronic cholecystitis. There is extreme subserosal fibrosis and a recent thrombus can be seen within a vessel. (Low power) (W U neg 52-4551)

the gall bladders after a single attack of cholecystitis. In other institutions where the percentage of free perforation into the peritoneal cavity is relatively high this fact is conditioned by the surgeons attitude In such an institution a surgeon would be conservative in operating on patients suspected of acute cholecystitis and in the treatment of patients with cholecystitis Such a conservative attitude would filter out the patients who recovered from gall bladder attacks and increase the number of patients coming to operation with serious complications thus in creasing the frequency of free perforation of the gall bladder Andrews demon strated that so-called empyema of the gall bladder usually consists of milky fluid which represents an emulsion of calcium carbonate or an emulsion of amorphous or

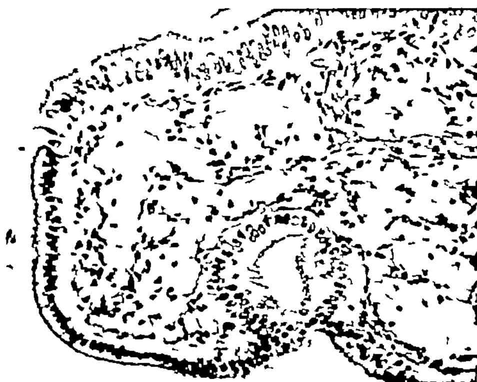


Fig 497 —Photomicrograph of cholesterosis of the gall bladder Beneath the normal epithelium of a villus are large foamy cells. (×400) (W U neg 50-976)

crystalline cholesterol Womack demonstrated that the injection of concentrated bile into the gall bladder produces acute cholecystitis. If cholesterol or pigment stones lie free within the gall bladder no inflammation is produced. Inflammatory changes in the gall bladder usually occur only when a single stone or stones are im pacted in the cystic duct (Mechling) Such impaction may interfere with the venous supply of the gall bladder by obstructing tortuous venous channels sur rounding the cystic duct. In 89 of 93 cases of acute cholecystitis reported by Hall endorf there were stones in or around the cystic duct. Interference with these venous channels may cause congestion of the gall bladder wall and even hemor rhagic infarction Under such circumstances the primary insult to the gall bladder is nonbacterial and bacterial invasion occurs only secondarily In children gall bladder disease is rare. Stones in the common duct are also unusual and therefore jaundice in a child practically never indicates choledocholithiasis (Uhn) Further

more if acute cholecystitis occurs it is often associated with some systemic infection such as hemolytic streptococcal septicemia and typhoid fever (Glenn)

In acute cholecystitis the clinical symptoms and signs are those of an acute inflammation in the right upper quadrant of the abdomen The decision as to when to remove the gall bladder has been long debated The concept of patient individualization recommended by Lahey seems logical. If the patient is thin, not critically ill and the gall bladder not too inflamed and thickened, its removal is indicated However in the aged obese patient with advanced acute inflammatory changes cholecystectomy might be not only difficult but dangerous. In such an instance cholecystotomy is the treatment of choice In an acutely distended gall bladder bile may leak through the intact wall and cause a peritoneal reaction.

Acute cholecystitis presents only slight thickening of the wall of the gall bladder and the mucosa is an angry grayish red color The pathogenesis is related to a stone impacted in the cystic duct Microscopic examination shows an intact mucosa, acute inflammation and subserosal edema and there are often recent thrombi within small veins. We have seen one instance of perforation which was secondary to a primary polyarteritis involving the wall of the gall bladder

CHRONIC CHOLECYSTITIS AND CHOLELITHIASIS

Chronic cholecystitis is usually not present in the absence of lithiasis, although lithiasis (cholesterol and pigment stones) may be present without chronic cholecystitis. In the extremely altered gall bladder the subserosal tissues of the wall almost invariably are greatly thickened (Figs 498 and 499) Stones are usually present, often of the mixed type True ulceration of the mucosa is infrequent. Microscopically the mucosa shows minimal to moderate chronic inflammation. The muscle may be hypertrophied and separated Diverticula are common and frequently there are excessive deposits of lipid in the intramural tissues, and stones may form in the wall (Weismann) If stones have become impacted in the cystic duct, hemorrhagic infarction of the wall can occur Bacterial invasion is secondary to such vascular alterations Small stones frequently travel through the cystic duct to become impacted in the ampulla of Vater or terminal third of the common duct where they cause severe colic and intermittent obstructive jaundice. Large stones can also become impacted in the small bowel often at the ligament of Treitz or at the ileocecal valve It has often been argued that all gall bladders which contain stones should be removed surgically because of the risk of cancer, the risk of cancer being greater (5 to 10 per cent) than the operative mortality (1 to 3 per cent) (Graham) This argument lacks validity at the present time. For instance at the Cleveland Clinic, Russell reported 29 cases of carcinoma of the gall bladder between 1932 and 1948. During this same time period there were 1 488 cholecystectomies which made the incidence of carcinoma only 1.9 per cent. The reasons for removing a gall bladder containing stones are concerned with the serious inflammatory and obstructive complications which arise from them, and not with the possibility of associated cancer (Jaguttis) Truesdell did exploratory laparotomies on 500 women for conditions other than gall bladder disease. Most of these patients had been pregnant sometime in the past. They were therefore

a favorable group to have gallstones He palpated the region of the gall bladder in this group and 50 (or 10 per cent) had gallstones. Subsequent history and follow up demonstrated that in only six were these truly silent stones.

The presence of gallstones may lead to *internal biliary fistulas* these are usually located between the gall bladder and the duodenum the gall bladder and the colon or the common bile duct and the duodenum over 90 per cent of the cases reported in the literature were in these locations (Waggoner) These fistulas are created by the formation of inflammatory adhesions between the gall bladder and adjacent organs and the subsequent erosion of a stone through the gall bladder



Figs. 498 and 499 —Gross photograph of two gall bladders with advanced chronic cholecystitis. In both, the subserosal portions are greatly thickened In one there is ulceration of the mucosal surface One gall bladder shows a single large stone and the other shows multiple faceted stones. (Fig 498 W U neg 50-2765 Fig. 499 W U neg 49-4576)

or its main duct into the gastrointestinal tract. Continuing choledochal obstruction contributes to the persistence of the fistula (Hicken) Fistulas can be diagnosed by a flat plate roentgenogram of the abdomen for at times air can be seen in the extrahepatic biliary system Moreover a gastrointestinal series or a barium enema may reveal the unexpected outlining of the biliary tree Fistulas may also become evident if the patient vomits or passes a large gallstone. In the cholecystocolic fistulas infection often is severe Repair of these fistulas requires cholecystectomy and closure or resection of the involved portion of bowel

Strictures of the common duct are usually caused by operative trauma in which the duct is excised or ligated inadvertently Anatomic variations of the ducts and

blood vessels may cause such an operative error (Eisendrath Flint) Strictures also occasionally are the result of infection following operation (Cole) Their repair is a difficult surgical procedure. When the ends of the duct can be located, excision of the stricture and end to-end anastomosis (Lahey) or anastomosis of the duct to the duodenum (Walters) are recommended. At times it may be necessary to anastomose the cut end of the hepatic duct to the jejunum (Lahey) Cole recommends the use of Roux-en Y choledochojejunostomy for many strictures of the common duct The operative removal of the gall bladder is subject to grave complications and should be undertaken only by surgeons with adequate training



Fig 500 —Epidermoid carcinoma of the gall bladder with almost complete replacement of the wall and infiltration of surrounding structures. There were stones present.

TUMORS

Benign tumors of the gall bladder are practically nonexistent. The rare epithelial adenoma can usually be visualized at the time of cholecystography Argentaffin cells can occur in the gall bladder which explains the rare presence of carcinoid tumors in that organ (Christie)

Cancer of the gall bladder and the extrahepatic ducts is an extremely serious disease Carcinoma of the terminal third of the common bile duct is discussed in the chapter on Pancreas and Periampullary Region (see page 485) In a few instances cancer may arise from the hepatic duct or at the confluence of the cystic and hepatic ducts. It is almost always discovered in an advanced stage. It occurs predominantly in women (ratio 5 to 1) usually over the age of 50 Russell reported 29 cases of carcinoma of the gall bladder among 1 488 cholecystectomies (an incidence of 1 9 per cent) During this period (1932 to 1948) a diagnosis of cholelithiasis by roentgenologic examination was made in 4 459 persons. Thus in the presence of cholelithiasis the incidence of carcinoma was 0 66 per cent. Carcinoma may not be diagnosed clinically but at the time of exploration of the gall

bladder for stones the diagnosis usually is evident Even when it is possible to resect the gall bladder in the presence of carcinoma practically no patients are cured (Jones) The only patients ever cured are those few in whom early cancer was found unexpectedly at pathologic examination Such cured cases might also include the papilloma of the gall bladder because three of four cases of papil lomas reported by Tabah also demonstrated focal carcinoma

Microscopically a gall bladder containing cancer shows extreme fibrosis of its wall Gall stones are present in 80 to 90 per cent of these gall bladders (Fig 500) Frequently the pathologist does not consider the diagnosis of cancer when there *is no ulcerating obviously cancerous mass* The carcinomas are *either adenocar* cinoma or squamous carcinoma. Squamous carcinoma occurs from metaplasia of columnar epithelium of the gall bladder The adenocarcinoma may secrete vari able amounts of mucin Unfortunately these carcinomas spread through the wall of the gall bladder and invade the liver the pericolic tissues and the lymph nodes and even infiltrate the duodenum Because of such extensions, it is nearly always impossible to excise them adequately

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Chapter 13

PANCREAS AND PERIAMPULLARY REGION

ACUTE AND CHRONIC PANCREATITIS

Pancreatitis has been and still is a clinical enigma and the subject of much controversy (Fitz) Its etiology is unknown Furthermore experimental work has been hampered by the fact that most laboratory animals do not suffer naturally from this illness in fact it has not been produced in animals short of direct pancreatic trauma.

Between 1920 and 1930 the diagnosis of pancreatitis was infrequently considered except at operation or postmortem examination both of which permitted pathologic examination. In the early 1930's the association of elevation of the serum amylase with the pathologic findings of pancreatitis was repeatedly observed. The concept grew that an elevated serum amylase alone would be adequate evidence of acute pancreatitis (Elman) As operations decreased in number the mortality associated with increase of serum amylase (and presumably therefore acute pancreatitis) also of course decreased

Duodenal ulcer volvulus gangrenous cholecystitis and mesenteric thrombosis may also be accompanied by elevation in serum amylase but, if these conditions are treated conservatively under the mistaken diagnosis of pancreatitis the pa

tients may die because of lack of operative interference. Even with early exploration of patients with an elevated serum amylase, it is often difficult to detect any disease process in the pancreas at all. For instance in 67 patients explored within six weeks of an attack of presumed pancreatitis, 50 had a serum amylase of 1000 or more Somogyi units 43 of these had biliary lithiasis with a grossly normal pancreas, 5 had lithiasis and pancreatitis and only 1 had pancreatitis alone (Criscione) Consequently, the notion that nonoperative treatment tends to improve mortality is fallacious when based on these figures These studies also suggest that the nonoperative treatment (medical or surgical) has not in any way influenced the usual unfavorable course of hemorrhagic or necrotizing pancreatitis.

At present, since gallstones are found in 80 to 90 per cent of the patients with increased serum amylase the erroneous inclusion of these cases with the fulminant cases of hemorrhagic pancreatitis will dilute the operative mortality rate.

Since conservative treatment is of questionable benefit in severe pancreatitis, and since serious lesions other than pancreatitis may cause elevated serum amylase, re-evaluation of the operative treatment is indicated based on the following principles immediate operation should be performed for signs of evident surgical catastrophe despite serum amylase elevations operation should be considered in the patient who remains status quo or in whom the clinical condition worsens after a period of improvement and elective exploration of the common bile duct should be performed at the optimal time in the clinical course of all patients who suffer from abdominal pain coupled with serum amylase elevation (Criscione)

If careful examination of the pancreas at operation is correlated with clinical findings and coupled with pancreatic biopsy our understanding of this complex problem might be clarified immeasurably

In mumps the pancreas is occasionally involved by the mumps virus (Brown) Longmire has cited two cases in which postmortem examination showed the same degree of pancreatitis in both the main pancreas and the heterotopic pancreas. The heterotopic pancreas was located in a Meckel's diverticulum in one in the jejunum in the other These two instances suggest some systemic disorder affecting pancreatic tissue regardless of its location Opie's famous case (1901) demonstrated pancreatitis associated with a small stone lodged in the ampulla The stone had converted the common bile duct and the main pancreatic duct (duct of Wirsung) into a common channel so that bile might have passed into the pancreatic duct and produced pancreatitis The theory that bile activates trypsinogen so that trypsin may digest the duct wall and allow pancreatic enzymes to digest the adjacent parenchyma is as yet unproved. Lipase splits fat and allows calcium soaps to form. Trypsin has the capacity to cause primary necrosis of the vessel walls leading to hemorrhage Although Opie's observation was valid, the formation of a common channel with a stone impacted in the ampulla occurs in only a small percentage of cases of pancreatitis (less than 5 per cent) As Dragstedt pointed out, the union of the pancreatic and bile duct to form an ampulla must occur at a sufficient distance from the duodenal opening to permit obstruction of the orifice without obstruction of either duct The stone must be just the right size for if it is too small it will not block the ampullary opening and if it is too large it will block either or both the common bile duct and pancreatic duct. In

1919 Archibald demonstrated experimentally that spasm of the sphincter of Oddi might produce a common channel Many studies have been made on autopsied cases to determine how often the anatomic setup would permit the common channel theory to operate. There are many anatomic variations in the ampullary area in which the formation of a common channel is not possible these include separation of common and pancreatic ducts by a septum and independent emptying of the pancreatic duct into the duodenum The consensus indicates that a common channel is possible in *50 to 60 per cent* of cases. Howard studied 50 fresh specimens of pancreas duodenum and common duct. When the papilla of Vater was obstructed by a small calculus or clamped by a hemostat, fluid injected into the common bile duct regurgitated into the duct of Wirsung in 81 (54 per cent) of the 150 specimens. Fresh rather than fixed specimens give the most accurate findings.

The pancreatic duct is visualized in about 25 per cent of the patients having postoperative T tube cholangiograms If a common duct T tube is in place and pancreatic secretin is injected intravenously almost pure pancreatic juice comes from the T tube (Colp Doubilet) If morphine is given spasm of the sphincter of Oddi occurs, and if radiopaque material is again injected through the T tube into the common duct there is an increase in the number of patients in whom the whole pancreatic duct system may be visualized. Nitrites relax the sphincter Hydrochloric acid causes spasm. Chemical studies of bile coming from the common duct or gall bladder commonly show pancreatic ferments. Bile may be seen in the peripancreatic tissues of patients operated on for pancreatitis, possibly because of rupture of a peripancreatic duct. These findings show that the common channel functions during life so that bile may enter the pancreatic duct system.

The secretory pressure of the gall bladder bile ducts and pancreatic ducts varies under different conditions. With physiologic need the pressure of either system may show prominent variation Pancreatitis often occurs after a heavy meal or in alcoholics. The anatomic arrangement of the duct of Santorini is important for it has no sphincter and if it communicates with the main duct of Wirsung the biliary tract pressure would dominate In Howard's anatomic study the duct of Santorini did not communicate with the duct of Wirsung in 54 (36 per cent) of 150 specimens. This arrangement was present in 44 of the 81 cases in which reflux could be demonstrated but in only 10 of the 79 cases in which no reflux occurred.

It appears that the common channel theory cannot be invoked in about 40 per cent of cases. Rich suggests that *increased secretion in the presence of partial block* of the ductal system may cause rupture of ductules and acini with liberation of pancreatic enzymes into the pancreas. He supports this attractive thesis by demonstrating partial squamous metaplasia of the ducts which might cause such a block. Such squamous metaplasia, however occurs commonly in the apparently normal pancreas of older persons.

Pancreatitis may occur with tumors of the periampullar area in the head of the pancreas. We have seen rare instances of pancreatitis accompanying primary vascular lesions of polyarteritis. After an operation particularly in the region of the pancreas the patient may suddenly die and be found to have an extensive

pancreatitis. Operative trauma may be the cause of such pancreatitis. Unsuspected pancreatitis also may be found at autopsy (Figs 501 and 502) Chronic pancreatitis with lithiasis usually is diagnosed by roentgenologic examination or at postmortem examination rather than in a surgical pathology specimen. In the two cases reported by MacKenzie, both patients were alcoholics and had intractable

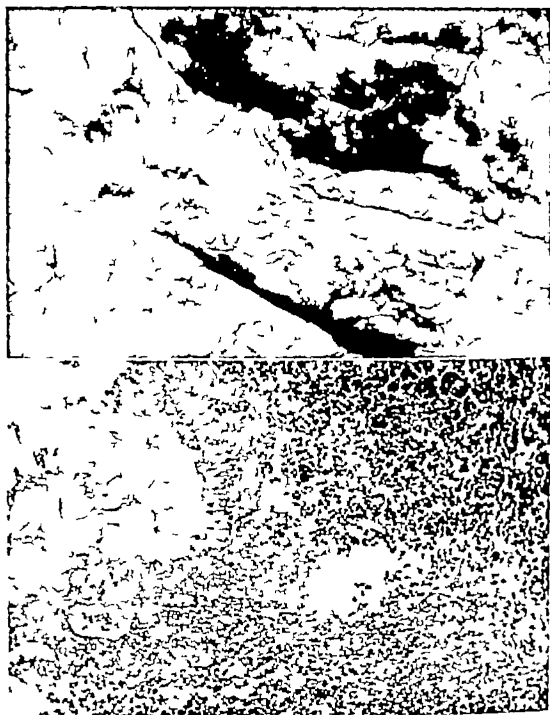


Fig 501.—Gross photograph of fat necrosis. Note well-defined areas of fat necrosis scattered over the mesentery (W U neg 49-2145)

Fig 502. Photomicrograph of fat necrosis in the pancreas (×140.) (W U neg 49-5441)

pain calcification of the pancreas and pancreatic insufficiency The commonest area for stone formation is in the duct of Wirsung within 2 to 4 cm of the ampulla of Vater (Edmondson)

ANNULAR PANCREAS

In this rare embryologic abnormality (about 90 cases reported) the ventral anlage of the pancreas fails to rotate properly (Baker Tendler) Encirclement of the duodenum by pancreatic parenchyma results and causes constriction of it. Pancreatitis may develop in association with this anomaly (Gross) Under these circumstances the duct in the annular pancreas originates anteriorly, courses to the right over the duodenum then posteriorly and to the left behind the duodenum, passing near the common duct (Lehman) These anatomic variations have to be kept in mind when operation is contemplated

HETEROTOPIC PANCREAS

Heterotopic pancreas is not rare (de Castro Barbosa) Busard found almost 550 cases in the literature. It is most common in the stomach (see chapter on Stomach) duodenum and jejunum, but it also occurs in the ileum Meckel s diverticulum, gall bladder omentum and in many other locations Grossly it suggests normal pancreas, but microscopically islet tissue is usually absent. Every pathologic change which occurs in the pancreas can occur in heterotopic pancreas (Chapman) In the stomach, heterotopic pancreas may even cause hemorrhage, ulceration or pyloric obstruction.

PSEUDOCYSTS

Congenital cysts of the pancreas are rare and are usually associated with cysts of other viscera such as liver or kidney Pseudocysts may be related to pan creatitis, or infrequently to trauma. Blockage of ducts leads to an accumulation of secretion and cyst formation These cysts often become large, spread beyond the substance of the pancreas into the lesser peritoneal cavity and present through the gastrocolic or gastrohepatic ligament. They do not have an epithelial lining The fluid within them has a high amylase content. If the cyst cannot be excised marsupialization of the cavity and sump drainage appears to be safe and effective More recently cystogastrostomy and cystojejunostomy have been recommended (Shumacker) However late complications such as hemorrhage and perforation have occurred (Rhoads)

EXFOLIATIVE CYTOLOGY

Biliary secretions have been aspirated in an attempt to diagnose lesions of the periampullary region but in most instances this method has failed. In only a few cases have definite small collections of tumor cells been identified (Lemon)

FROZEN SECTION

Frozen sections for lesions of the periampullary area and pancreas are often difficult. A correct diagnosis requires the cooperative efforts of both the pa thologist and the surgeon The pathologist should remember that the operative

pancreatitis Operative trauma may be the cause of such pancreatitis. Unsuspected pancreatitis also may be found at autopsy (Figs 501 and 502) Chronic pancreatitis with lithiasis usually is diagnosed by roentgenologic examination or at postmortem examination rather than in a surgical pathology specimen. In the two cases reported by MacKenzie both patients were alcoholics and had intractable

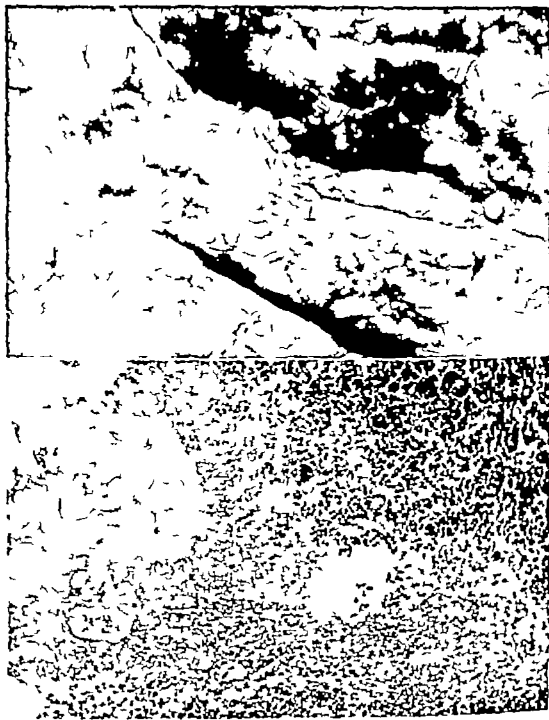


Fig 501 — Gross photograph of fat necrosis Note well-defined areas of fat necrosis scattered over the mesentery (W U neg 49-?145)

Fig 502 – Photomicrograph of fat necrosis in the pancreas. (×140) (W U neg 49-5441)

mortality for carcinoma of the head of the pancreas and periampullary area is very high (25 per cent) even in the hands of experienced surgeons. He must recognize that carcinoma in the head of the pancreas is practically never cured by surgery (no three year survivals at Barnes Hospital) while favorable results may follow resection of tumors of the ampulla and the terminal third of the common bile duct. The pathologist should not make a diagnosis of carcinoma from a frozen section unless he is absolutely certain There are many reasons for the difficulty in making a frozen section diagnosis Sections can easily be taken from an area of the head of the pancreas containing no tumor It may be difficult to distinguish well-differentiated adenocarcinoma from normal pancreatic ducts, but nerve sheath invasion if present is unequivocal evidence of carcinoma. Chronic pancreatitis simulates carcinoma because it makes the head of the pancreas hard. This hardness is due to inflammation and fibrous fixing of the lobules, but representative sections should be easy to interpret Accessory pancreatic ducts forming acini may be present between muscle bundles and be erroneously interpreted as carcinoma (Loquvam) Pancreatitis with obstruction of the ducts may lead to almost complete disappearance of pancreatic lobules leaving the dilated ducts, fibrous tissue inflammation and islet tissue The fibrosis and inflammation cause so much distortion that the lesion may look malignant With some degree of obstructive jaundice and no microscopic evidence of carcinoma in the head of the pancreas, it is mandatory that the duodenum be opened at exploration. A carcinoma arising in the ampulla often forms a papillary mass and sections taken from the surface may demonstrate well-differentiated papillary glandular lesions. The latter finding does not mean that the tumor is benign, for deep sections usually show more undifferentiated areas. If the carcinoma arises from the terminal third of the common bile duct it may be difficult to obtain representative tissue. Benign tumors in the ampullary region occur rarely These require only local excision. With experience however frozen section is highly accurate (Spjut)

During exploration of the jaundiced patient in whom obvious metastases are not present, the securance of histologic proof of carcinoma can be difficult. The head of the pancreas should be mobilized and carefully palpated, and the common duct should be exposed and its size determined. If a mass is felt in the head of the pancreas away from the ampullary region, direct incisional biopsy is done. Experience is required to avoid the common duct the gastroduodenal artery and the portal vein If frozen section of this specimen shows only fibrosis and the common duct is dilated, the duct should be explored. If choledocholithiasis is not present to explain the findings then duodenotomy should follow *Dilatation of the common duct and of the gall bladder in the presence of jaundice, and in the absence of biliary tract stones is almost always caused by carcinoma.* Transduodenal biopsy or biopsy of the head of the pancreas should be performed with care being taken to prevent duodenal spillage or excessive bleeding from the biopsy site so that possible seeding of the surrounding area by tumor cells can be avoided.

Once the diagnosis of cancer is established, operability must be determined. In most instances this depends upon whether or not the portal vein is free of neoplastic invasion. Exposure of the portal vein above and below the pancreas is

carried out and the pancreas is dissected free of the anterior surface of the portal vein by careful blunt dissection This is only possible in the absence of neoplastic involvement of the portal vein If this maneuver shows the portal vein to be free of tumor resection of the head of the pancreas can proceed Even though the anterior surface of the portal vein is found to be free of tumor, cancer may invade occasionally the posterior wall of the portal vein from the region of the uncinate process It is very difficult to determine whether or not the latter exists prior to the performance of a major portion of the resection If the cancer is found inoperable because of invasion of the portal vein or local metastases, cholecystojejunostomy is all that is indicated.



Fig 503—Benign adenomatous polyp of the ampulla producing almost complete obstructive jaundice. Removal resulted in complete relief of symptoms. (W U neg 52 193)

TUMORS OF THE PERIAMPULLARY REGION

Benign Tumors of the Ampulla

Practically no benign tumors of the ampulla exist but a few instances of epithelial adenomas have been described (Cattell) We have seen one causing partial biliary obstruction. Frozen section revealed a benign adenoma which was treated by local resection (Fig 503)





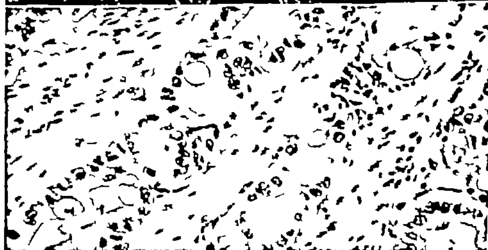


Fig 504 —Gross photograph of c rcinoma of the ampulla The probe is in the common duct and has its exit in the ampulla

Fig 505 —The common duct has been opened The tumor has blocked the ampulla and dilated the common duct

Fig 506 —Photomicrograph of a well-differentiated adenocarcinoma of the ampulla. In spite of its localized character this cancer rather quickly locally recurred. (Courtesy Dr Franz Leidler Veterans Hospital Jefferson Barracks, Mo)

CARCINOMA OF THE PERIAMPULLARY REGION EXCLUSIVE OF PANCREAS

Carcinomas are much less common in the periampullary region than in the pancreas, but in spite of a low incidence they are important because they are so much more curable than the carcinomas of the head of the pancreas. Tumors of this area can arise from the terminal third of the common bile duct from the lining epithelium of the intestinal mucosa, from the true ampulla, and under exceedingly rare circumstances from Brunner's glands (Figs. 504-506). Grossly



Fig. 507.—Photomicrograph of papillary carcinoma of the ampulla. (Low power.) (W. U. neg. 48-6358.)

carcinoma of the terminal third of the common bile duct usually infiltrates the surrounding tissues, replaces the wall of the bile duct, extends upward beneath its mucosa and extends downward to involve the wall of the duodenum. The opened common bile duct is greatly thickened and the mucosal surface has a granular appearance. The carcinomas which arise from the ampulla or from the lining epithelium of the distal common bile duct usually develop soft papillary masses in

the duodenal lumen which because of their softness may not be felt through the unopened duodenum (Fig 507) Grossly they show a papillary somewhat arborescent surface Near their base they are often quite firm

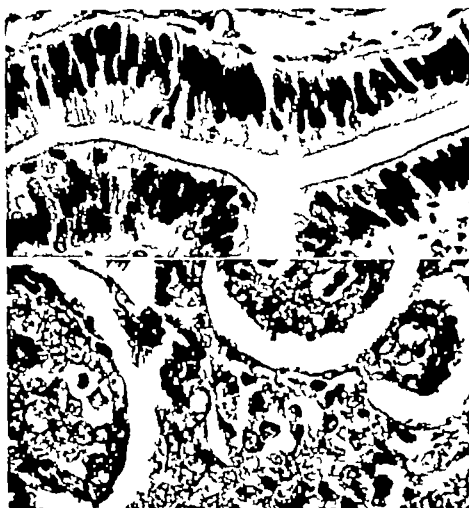


Fig 508 —Photomicrograph of section taken from the surface of the tumor shown in Fig 507 This shows only questionable evidence of carcinoma with stratification of cells and loss of nuclear polarity (×400) (W U neg 48-6332)

Fig 509 —Sections from the deepest portion of tumor show a highly undifferentiated carcinoma. (×400) (W U neg 48-6333)

Microscopically carcinoma of the terminal third of the common bile duct is usually a fairly well-differentiated adenocarcinoma, rarely an epidermoid carcinoma. The papillary tumors of the ampulla or intestine are made up of well defined glands resembling the lining epithelium of the mucosa of the intestine (Fig 508) The deeper portions of these tumors are often poorly differentiated (Fig 509) Nerve sheath invasion may be present.

In the study of specimens from the periampullary region very careful dissection of the main pancreatic duct and the common bile duct must be done to preserve the anatomic relationships in the periampullary region Sections should be carefully taken and oriented so that the extent and origin of tumor can be delineated It is imperative also to search for lymph nodes within the specimen.

Miller reported 30 carcinomas arising from the ampullary area Although th tumors appeared locally resectable the 7 patients surviving transduodenal res tion are either dead or dying By contrast in 11 patients with carcinoma of t ampulla surviving radical resection, 7 are living without disease.

ISLET CELL TUMORS

Islet cell tumors make up a small fraction of all pancreatic neoplasms. Th are found only rarely at postmortem examination, possibly because intensive sear for them is seldom made These functioning islet cell tumors give all the sym toms expected from an overdosage of insulin The patient's blood sugar may dr so low that he goes into convulsions or becomes so irrational he is thought eligil

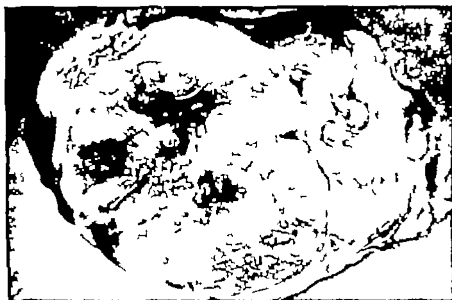


Fig 510—Gross photograph of functioning partially encapsulated islet-cell adenoma of t pancreas (W U neg 51 1694)

for confinement in a psychiatric institution Loss of consciousness mental co fusion, weakness and fatigue and convulsions occur with the episodes of hyp glycemia associated with this tumor Whipple's triad should be fulfilled before t clinical diagnosis of hyperinsulinism is tenable. This triad consists of (1) sym toms and signs of hypoglycemia usually induced by fasting or exercise (2) fa ing blood sugar levels below 50 mg per cent and (3) relief of symptoms by t administration of glucose. However before the diagnosis of an islet cell tum can be made, other causes of hypoglycemia should be eliminated Islet cell tumc are most frequently found in the body and tail of the pancreas. They are multip in about 12 per cent of patients. We have had one patient who had 3 pancreat resections for functioning islet cell tumors the entire pancreas was finally remove A total of fourteen islet cell tumors associated with hyperplasia of islet tissue we found The patient was cured

Grossly islet cell tumors vary in appearance. The more cellular of them ha a pinkish cast and may resemble spleen or a congested lymph node (Fig 510

Tumors of long duration occasionally have a great increase of fibrous connective tissue which may even contain calcium and bone. They do not have a well-defined capsule. In rare instances these functioning islet cell tumors may be malignant.

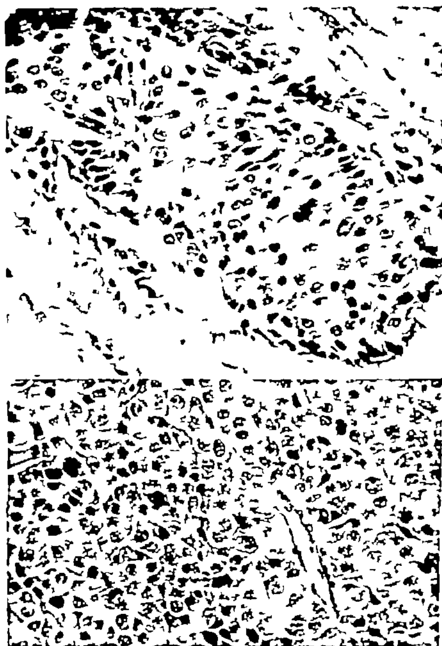


Fig 511 —Islet-cell tumor with blood vessel invasion. It measured 9 by 3.5 cm. and weighed 500 grams. It contained bone and showed a dense incomplete fibrotic capsule. Blood vessel invasion is demonstrated There were signs of hyperinsulinism. (×400) (W U neg 52 1833)

Fig 512 —Eight years later symptoms recurred The patient was explored, and tumor was present in the liver The patient died a few months later Well-differentiated tumor cells are replacing liver parenchyma. (×370) (W U neg 52 1834)

Evidence of malignancy is the presence of metastases in regional lymph nodes or the liver Microscopically these tumors should be studied after fixation in a solution such as Bouin's The tumor cells resemble normal islet cells and are arranged

in small clusters or columns separated by fibrous tissue with a variable degr vascularization This increased fibrosis with the epithelial distortion and the of encapsulation may cause an erroneous diagnosis of carcinoma. Multiple tions must be taken in order to demonstrate the presence or absence of vei vasion. It has now been demonstrated that if true vein invasion is present (ti thrombi fixed in the wall), it is significant The first reported case of nonf tioning islet cell tumor in which vein invasion was the only evidence of malig change exhibited metastases to the liver five years after the original oper: (Whipple) The patient lived another five years. We also have a patient in w true vein invasion was present in a functioning islet cell tumor (Fig 511) E years after operation the patient returned with liver metastases which were se ing insulin (Fig 512) When functioning islet cell carcinoma recurs or m tasizes signs of increased function also appear

Ellison has reported a syndrome of fulminating and fatal peptic ulcer as ated with noninsulin producing islet cell tumors. In these instances most of tumors are malignant, in 24 collected cases only 5 were benign. Ten out of 24 were multiple. The associated ulcers also appeared in atypical locations

CARCINOMA

Carcinomas of the pancreas occur in either the head or close to the hea about two thirds of instances the other third arises in the body and tail. cinoma of the body and tail grows insidiously provokes widespread metastases, often gives bizarre clinical signs and symptoms. In about 25 per cent of insta there are peripheral venous thrombi (Sproul) These tumors are only r: operable and therefore are not often available as surgical specimens. Carcin of the head of the pancreas because of its strategic location in relation to main extrahepatic ducts usually causes progressive jaundice which is associ with pain in at least one half the patients Grossly these tumors are poorly lineated, quite firm, and on cross section usually show yellowish-gray areas high percentage of them arise from the epithelium of the ducts rather than f the acini so that the involved ducts frequently become greatly dilated and plug with necrotic tumor This dilation may extend for a considerable distance bey the main mass of the tumor Because of ductal occlusion the surrounding lob tissue may be completely destroyed. In a few instances in which the tumor a from the acinar epithelium, there is complete obliteration of the architectur the pancreas without dilatation of the pancreatic ducts. Microscopically the mors which arise from the duct of the pancreas are often well-differentiated ad carcinomas. It may be difficult to decide whether or not there is a malign tumor present (Fig 513) Close attention has to be paid to the cytologic det The neoplastic epithelium lining the ducts shows considerable stratification of nuclear polarity unusual nuclear changes, and mitotic aberrations. This plastic epithelium may extend to the point of transection of the pancreas. carcinomas which arise from the acinar epithelium are made up of undifferentia rather small cells which usually resemble the cells of normal acini. This tu infiltrates quickly all the surrounding structures Because carcinoma of the h

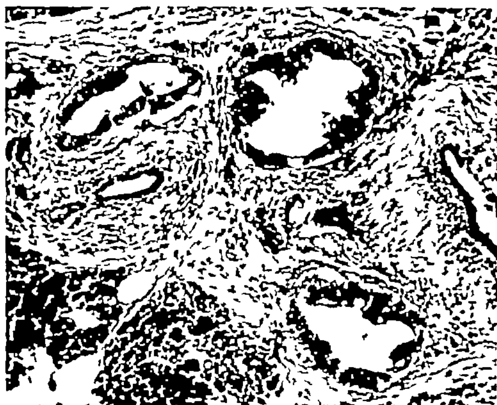


Fig 513 —Photomicrograph of the well-differentiated adenocarcinoma arising from the pancreatic duct with resultant fibrosis of the lobular tissue (×70) (W U neg 48-6476.)



Fig 514 —Photomicrograph of nerve shea a well-differentiat noma of the pancreas. (High U neg 48-6337)

of the pancreas extends along the ducts and invades the surrounding tissues often with involvement of the nerve sheaths and regional nodes radical surgery is usually not feasible and practically never results in cure (Fig 514)

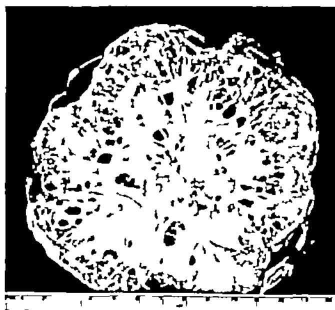


Fig 515 —Gross photograph of a cystadenoma of the pancreas. Note radiating fibrous bands. (From Haukol R. S Am. J Roentgenol 63 234 245 1950)



Fig 516 —Photomicrograph of cystadenoma of the pancreas demonstrating cystic spaces lined by cuboidal epithelium and fibrous stroma. (×200) (W U neg. 50-3764) (Slide courtesy Dr R. S Haukol.)

CYSTADENOMA AND CYSTADENOCARCINOMA

Cystadenoma of the pancreas is a rare slowly growing true neoplasm which occurs predominantly in females. This tumor usually arises in the body or tail of the pancreas where it may reach an extremely large size. Diabetes may be associated with the lesion when the abundant islet cell tissue of the tail of the

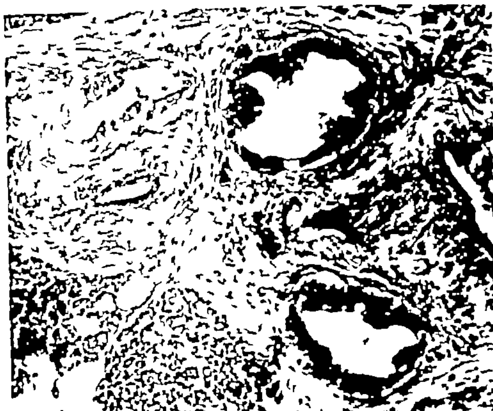


Fig 513 —Photomicrograph of a well-differentiated adenocarcinoma arising from the pancreatic duct with resultant fi[illegible] of the lobular tissue (×70) (W U neg 48-6476.)

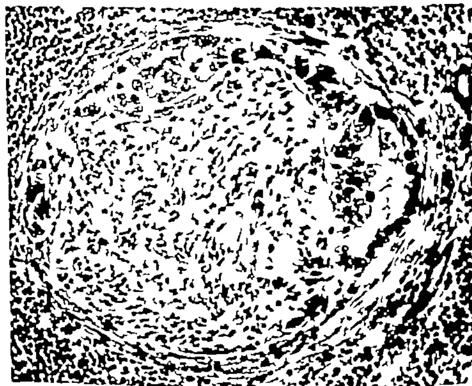


Fig 514 —Photomicrograph of nerve sheath invasion in a well-differentiated adenocarcinoma of the pancreas. (High power) (W U neg 48-6337)

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Fig 516 — Photomicrograph of cystadenoma of the pancreas demonstrating cystic spaces lined by cuboidal epithelium and fibrous stroma. (×200) (W U neg 50-3764) (Slide courtesy Dr R. S Haukol)

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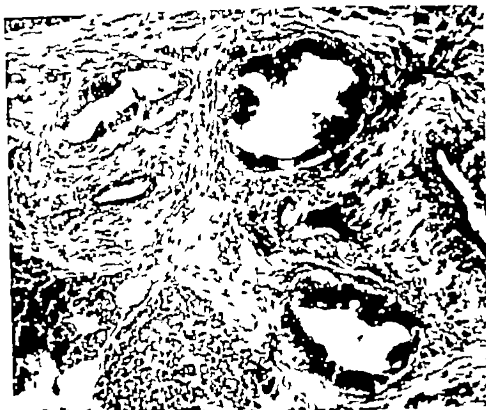


Fig. 513.—Photomicrograph of th ll-differentiated adenocarcinoma arising from the pancreatic duct with resultant fibr f the lobular tissue (×70.) (W U neg 48-6476.)

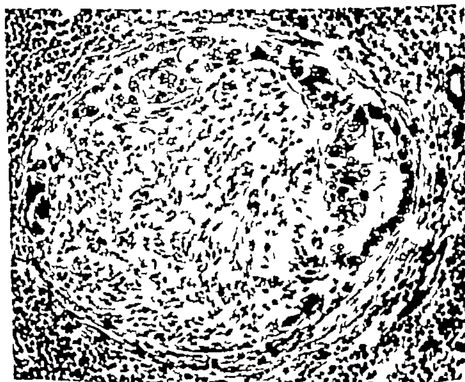


Fig 514.—Photomicrograph of nerve sheath invasion in a well-differentiated adenocarcinoma of the pancreas. (High power.) (W U neg. 48-6337.)

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Fig 515 —Gross photograph of a cystadenoma of the pancreas Note radiating fibrous bands. (From Haukol R S Am J Roentgenol. 63 231 245 1950)



Fig 516 —Photomicrograph of cystadenoma of the pancreas demonstrating cystic spaces lined by cuboidal epithelium and fibrous stroma. (×200) (W U neg 50-3764) (Slide courtesy Dr R. S Haukol)

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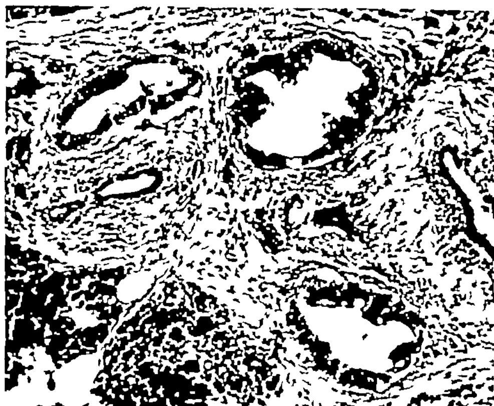


Fig 513 —Photomicrograph of the well-differentiated adenocarcinoma arising from the pancreatic duct with resultant fibrosis of the lobular tissue (×70) (W U neg 48-6476.)

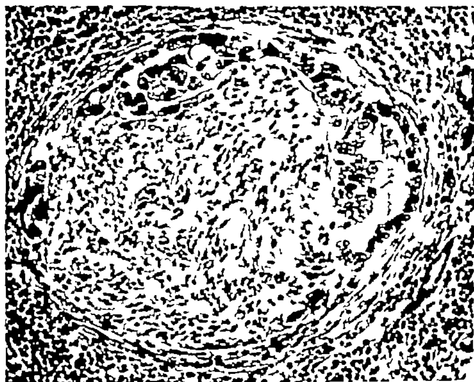


Fig 514 —Photomicrograph of nerve sheath invasion in a well-differentiated adenocarcinoma of the pancreas. (High power) (W U neg 48-6357)

of the pancreas extends along the ducts and invades the surrounding tissues often with involvement of the nerve sheaths and regional nodes radical surgery is usually not feasible and practically never results in cure (Fig 514)



Fig 515 —Gross photograph of a cystadenoma of the pancreas Note radiating fibrous bands (From Haukol R. S Am. J Roentgenol. 63 234-245 1950)

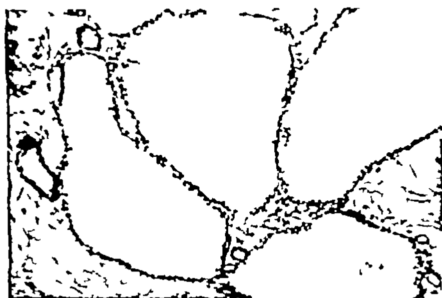


Fig 516 —Photomicrograph of cystadenoma of the pancreas demonstrating cystic spaces lined by cuboidal epithelium and fibrous stroma. (×200) (W U neg 50 3764) (Slide courtesy Dr R. S *Haukol*)

CYSTADENOMA AND CYSTADENOCARCINOMA

Cystadenoma of the pancreas is a rare slowly growing true neoplasm which occurs *predominantly in females. This tumor usually arises in the body or tail* of the pancreas where it may reach an extremely large size Diabetes may be associated with the lesion when the abundant islet cell tissue of the tail of the

pancreas is destroyed by the tumor On section the tumor is usually multilocu lated. The trabeculae between the locules may show calcification which appear radiologically as a radiating pattern (Haukohl) (Fig 515) Fluid within the locules is often viscid or gelatinous. Microscopically these tumors are lined by cuboidal or tall columnar epithelium which resembles to a great extent the lining epithelium seen in pseudomucinous cysts of the ovary (Fig 516) They are usu ally benign but under rare instances become malignant (Jemerin) Surgical re moval is the treatment of choice (Benson)

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Chapter 14

ADRENAL GLAND

INTRODUCTION

The cortex and medulla of the adrenal gland have entirely different origins. The cortex arises from mesoderm, and the medulla from ectodermal chromaffin tissue. Heterotopic adrenal cortical tissue has been reported in numerous locations. The most common site is in the region of the adrenal gland. It occurs occasionally in the region of the celiac plexus (Graham) within the kidney substance and along the course of the spermatic and ovarian veins. Only rarely has it been seen within the testes (Nelson) or ovary. This heterotopic tissue is found usually in the broad ligament near the ovary or close to the tail of the epididymis. Stout has seen heterotopic adrenal tissue in the canal of Nuck, in hernial and hydrocele sacs in the mesentery of the appendix, and in the retroperitoneal area. Whether it ever develops in the liver is doubtful.

CLASSIFICATION

An excellent classification of the tumors arising from the adrenal cortex has been devised by Cahill. This classification has been modified because of refinements in laboratory diagnosis. *The tumors are less likely to have a pure syndrome* than the hyperplasias.

A Arising from cortex
  1 No recognizable hormonal change
  2 Changes due to excess androgens
    a In female child toward adult masculinity
    b In female adult toward masculinity
    c In male child toward adult masculinity
  3 Changes due to excess estrogens
    a In adult male toward femininity
    b Sexual precocity in female child
  4 Mixed syndromes
    a Cushing's syndrome with virilism
    b Aldosteronism with Cushing's features
  5 Cushing's syndrome
B Arising from medulla
  1 Neuroblastoma
  2 Ganglioneuroblastoma
  3 Ganglioneuroma
  4 Pheochromocytoma

Focal nodular areas of hyperplasia of the adrenal cortex and cortical adenomas are often discovered at postmortem examination The number of such adenomas increases with the age of the patient but they are not correlated with hypertension diabetes or cardiovascular disease Adenomas greater than 3 mm in size were encountered in 216 (2.86 per cent) of 7 437 consecutive autopsies (Commons) These adenomas have no clinical significance

TUMORS OF THE ADRENAL CORTEX WITHOUT RECOGNIZABLE HORMONAL CHANGES

These tumors are rare frequently malignant and often large. They may weigh as much as 1 000 grams before discovery The tumor is often encapsulated and on section shows multiple bright yellow nodules. Areas of necrosis within such tissue are frequent (Figs 517 and 518) Whether the tumor is benign or malignant may be difficult to evaluate microscopically (Cottler) Individual cells closely resemble the cortical cells of the adrenal cortex and have eosinophil staining cytoplasm and well-defined nuclei Bizarre large nuclei do occur often with aggregations of chromatin Blood vessel invasion is common this finding is an indication of malignant change (Fig 519) Hemorrhage and necrosis within malignant neoplasms often cause fever suggesting that the patient has an infection (Wood)

TUMORS OF THE ADRENAL CORTEX WITH CHANGES DUE TO EXCESS ANDROGENS

Androgenic changes resulting from tumor occur in three categories of patients in female children toward adult masculinity in male children toward adult masculinity and in female adults toward masculinity (Fig 520) When virilism occurs in the adult female it is more commonly due to neoplasm than to hyperplasia. The adrenogenital syndrome occurs before puberty in 50 per cent of patients 83 per cent of them are females (Heinbecker) These tumors are variable in size and



Fig. 517.—Retrograde pyelogram of a 47 year-old male patient with a large asymptomatic tumor of the right adrenal displacing the right kidney (W U neg 50-2916.)

Fig 518.—Gross photograph shows a large bright yellow tumor encapsulated with areas of necrosis. Weight, 900 grams (W U neg 50-2656)

Fig 519.—Photomicrograph demonstrates large cells with considerable variations in size and with many bizarre nuclei. There were tumor cells lying free within veins. This finding was apparently significant, for two years after surgical removal the patient developed pulmonary metastases. (×450) (W U neg 50-2858.)

more often benign than malignant Their gross and microscopic appearance is no different from the nonhormone producing tumor

Patterson and Allen have devised a simple chemical test which is helpful in the diagnosis of this group of virilizing tumors They demonstrated in both female pseudohermaphrodism and virilizing tumor that there is an increase of ketosteroids in the urine However in virilizing tumors of the adrenal cortex there is a specific 17 ketosteroid designated as dehydroisoandrosterone which is present in sufficient amount to be identified by the Allen blue test, this test is not positive in cases of adrenal hyperplasia or of female pseudohermaphrodism. Interstitial cell tumor of the testis arrhenoblastoma of the ovary, or simple hyperplasia of the adrenal cortex all cause virilization In these situations Patterson and Allen s tests may be helpful diagnostically



Fig 520 —Virilizing changes in an adult woman with a huge adrenal cortical tumor weighing over 1,000 grams Microscopically it appeared similar to the one shown in Fig 519 This patient remained free from recurrence for five years but in the sixth year she died of recurrent disease (FFSCH 47 10379)

TUMORS OF THE ADRENAL CORTEX WITH CHANGES DUE TO EXCESS ESTROGENS

Feminization in an adult male is the rarest form of endocrine abnormality caused by adrenal cortical tumor (Simpson) Practically all of these tumors are malignant (Armstrong) The younger patients all die quickly the older group survive only slightly longer Of the eight cases reported by Armstrong only one was possibly cured These patients showed an increased output of 17 ketosteroids a gross excess of urinary estrogens was demonstrated in two

Again the gross and microscopic findings are not helpful in differentiating the hormonal abnormality Broster believes that in feminism fuchsinophilic granules occur in the tumor cells (demonstrated by Masson Trichrome stain) In adrenal virilism the cortical cells (demonstrated by Ponceau fuchsin stain) contain a vivid

red granular material in their cytoplasm (Broster) However Cahill was not able to confirm these findings. He felt that the tumors which produce endocrine changes have cells which resemble most the reticular layer of the adrenal and have increased fuchsinophilic granules.

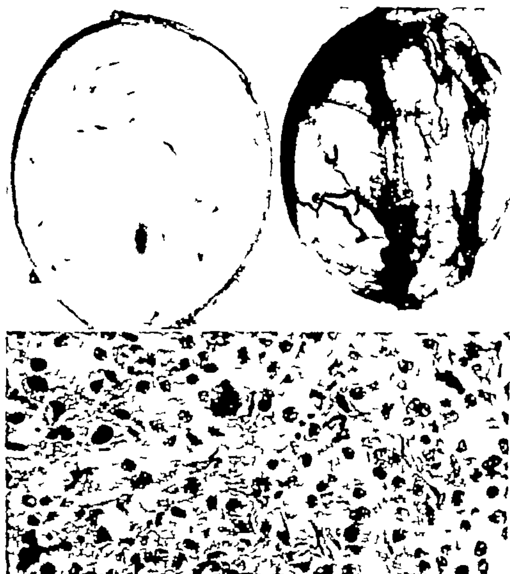


Fig 521 —Gross photograph of a small cortical adenoma of the adrenal which was causing virilizing signs. This tumor was identified by perirenal air insufflation. (W U neg 49-6852.)

Fig 522 —Photomicrograph of the tumor shown in Fig 521 with large cells and atypical nuclei. Virilizing signs and symptoms rapidly regressed. Patient has remained well for three years. (×480) (W U neg 49-6714)

CUSHING S SYNDROME

Cushing s syndrome without sexual changes can occur in both males and females. Clinical demonstration of tumor may be impossible Eighty per cent of the patients are females and in 20 per cent the syndrome occurs before puberty (Fig 523) Various endocrine changes may simulate Cushing s syndrome other than tumors of the adrenal cortex.

It is possible in some instances to demonstrate the presence of tumor by retrograde pyelography. Plain films of the abdomen and intravenous pyelography gave evidence of neoplasm in 10 of 13 cases reported by Heinbecker. Perirenal oxygen insufflation is a valuable diagnostic procedure which in Cahill's hands has proved to be without risk. In a patient with Cushing's syndrome without identifiable tumor, adrenal exploration should be transabdominal. If the adrenal is atrophic, tumor probably is present on the opposite side (Fig. 524). If one adrenal is normal or hyperplastic, the other will rarely contain tumor. Frozen section will not help to determine whether an adrenal is atrophic or hyperplastic.



Fig. 523.—Clinical photographs of a child with Cushing's syndrome 7 months before development of the tumor, with the tumor at age of 17 months, and after successful operation at the age of 27 months. The child remains well two and one-half years later. (W U negs. 56-5729, 56-558 and 56-559.) (From Heinbecker, P., O'Neal, L. W., and Ackerman, L. V.: Surg. Gynec. & Obst. 105: 21, 1957. By permission of Surgery, Gynecology & Obstetrics.)

Primary aldosteronism may be due to an adrenal cortical tumor. This tumor secretes excessive amounts of aldosterone, resulting in urinary loss of potassium with retention of sodium. The diagnosis of this condition may be difficult, particularly if no tumor can be identified radiographically. If needle biopsy shows a normal kidney, a diagnosis of primary aldosteronism is likely (Milne).

When adrenal cortical hyperplasia rather than neoplasm is the cause of Cushing's syndrome, it is possible to cause regression of the signs and symptoms by resection of adrenal tissue (Priestley). All of one adrenal and most of the other adrenal is removed (Fig. 525). Hyperplasia is five times more common than neoplasm in patients with Cushing's syndrome (Sprague). The accompanying photomicrograph (Fig. 526) demonstrates the hyperplasia and hypertrophy of adrenal cortical cells.

In the past the removal of an adrenal containing a neoplasm often resulted in a high operative mortality rate because the opposite adrenal was atrophic and therefore functioning at a low level (Fig. 527). This atrophy was less common in the adrenogenital syndrome (29 per cent) than in Cushing's syndrome (73 per cent) (Rapaport). Today with the use of steroid replacement therapy, postoperative mortality is much lower.

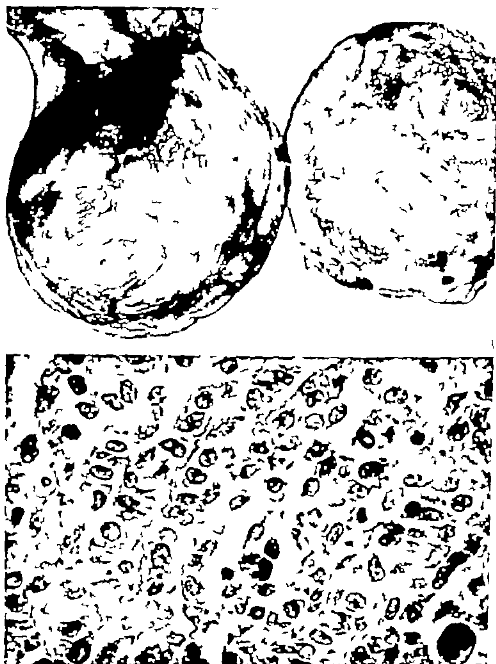


Fig 524 —Gross and microscopic appearance of the tumor causing Cushing's syndrome in Fig 523 This was a cortical tumor possibly malignant with considerable pleomorphism of the tumor (W U neg 56-709) (×560 W L neg 57 3686) (From Heinbecker P, O Neal, L. W and Ackerman, L V Surg Gynec & Obst. 105: 21 1957 By permission of Surgery Gynecology & Obstetrics.)



Fig 525.—Gross photograph of tissue removed for Cushing's syndrome in cortical hyperplasia. All of one adrenal and most of the other is present. Total weight was 12.5 grams. (W U neg 55 1113)

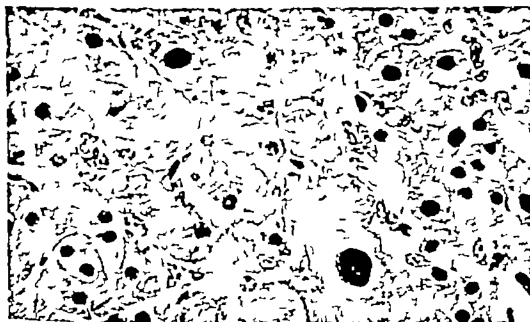


Fig 526.—Photomicrograph of adrenal cortical hyperplasia in a patient with Cushing's syndrome Note large cells with bizarre nuclei (×400) (W U neg 52 2480)

TUMORS OF THE ADRENAL MEDULLA, NEUROBLASTOMA, AND RELATED TUMORS

Tumors of chromaffin tissue occur most commonly in the adrenal medulla of young children but are seen in heterotopic areas such as the regions about the adrenal, the bifurcation of the aorta (Zuckerkandl's gland) and at times the posterior superior portion of the mediastinum. Grossly these tumors are hemorrhagic and more often small than large they frequently contain foci of calcification (Fig 528) These tumors occur rarely in older persons and have the same gross appearance but show a greater cellular differentiation evidenced by collections of ganglion cells as well as poorly differentiated cells such as sympathicoblasts. The

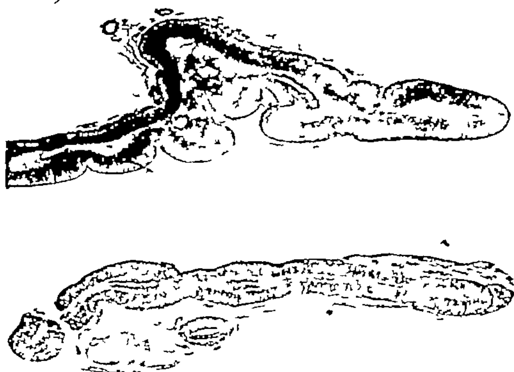


Fig. 527 —Photomicrograph demonstrating contrast between a normal adrenal from a 5-month-old girl and a markedly atrophic adrenal which was contralateral to a functioning carcinoma in a 7-month-old girl. (Low power) (W U negs 56-5919 and 56-5920)

microscopic pattern of a neuroblastoma shows collections of cells with uniform, deeply staining nuclei slightly larger than lymphocytes (Fig 529) There is little cytoplasm, and cytoplasmic outlines are poorly defined. Necrosis usually is present with tumor cells grouped around blood vessels. In the poorly differentiated tumor there are well-defined rosettes However better-differentiated zones in which the nuclei are larger and have fine chromatin are frequent. In this latter group there is a fine fibrillar cobwebby network between masses of cells focal areas of calcification may be seen (Wahl) (Fig 530) Collections of ganglion cells which are often multinucleated can be seen in still better-differentiated areas. Infrequently well differentiated ganglioneuromas occur similar to those described in the posterior

nediastinum. Tumors of a similar nature may arise in any of the heterotopic ocations mentioned.

LINICOPATHOLOGIC CORRELATION

Tumors of the adrenal medulla spread rapidly to the liver, bones, orbit and kull. They often grow in grapelike masses on the surface of the pleura and involve he lung. These tumors are extremely radiosensitive and may be cured by small mounts of irradiation even in the presence of metastases to the liver. Wittenborg reported 73 cases of neuroblastoma of which 45 received some form of treatment. Twenty two patients have survived three or more years. There were 6



ig 528 —Gross photograph of hemorrhagic neuroblastoma with zones of necrosis (EFSCH)

patients with metastases to the liver; these 6 are surviving three years with irradiation alone. It has also been reported by Murray that tissue culture for neuroblastoma is an absolute method of making a diagnosis within twenty four hours because recognizable neurites appear.

PHEOCHROMOCYTOMA

Pheochromocytomas may or may not produce adrenaline like material (Beer). About 200 endocrinologically active cases have been reported. These are rarely

TUMORS OF THE ADRENAL MEI AND RELATED TUMORS

Tumors of chromaffin tissue occur young children but are seen in hetero adrenal, the bifurcation of the aorta (Z terior superior portion of the mediastini and more often small than large, they f 528) These tumors occur rarel, in old ance but show a greater cellular differ ghon cells as well as poorly different



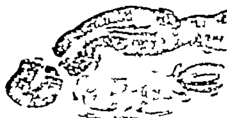


Fig 527 —Photomicrograph dem a 5-month-old girl and a markedly atro carcinoma in a 7 month-old girl. (Lo



microscopic pattern of a neurobla deeply staining nuclei slightly larg cytoplasm and cytoplasmic outline with tumor cells grouped around b there are well-defined rosettes. H nuclei are larger and have fine chr is a fine fibrillar cobwebby network tion may be seen (Wahl) (Fig 530 multinucleated can be seen in still differentiated ganglioneuromas occ



Fig 531 Gross photograph of a [illegible] yellowish white pheochromocytoma Remnant of normal adrenal gland can be seen This tumor appeared in a patient with von Recklinghausen's disease (W U neg [illegible] ×10)

Fig 532 Photomicrograph of a functioning pheochromocytoma Note delicate vessels surrounding groups of cells and lack of mitotic activity The intense granularity of the cytoplasm is due to a positive reaction to chromate (×600) (W U neg 58-4083)

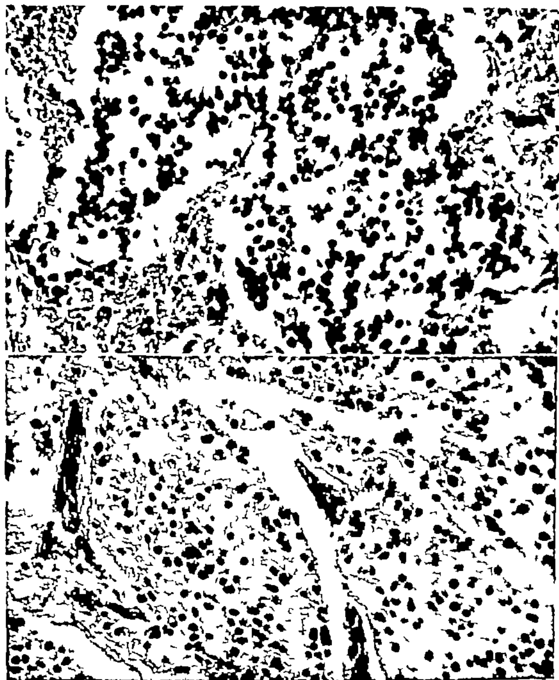


Fig 529—Photomicrograph of typical neuroblastoma with poorly defined rosettes. (×360) (W U neg 50-446)

Fig 530—Photomicrograph of ganglioneuroblastoma. Note fine fibrillar network between cells. (×330) (W U neg 51 1658)



Fig 531 —Gross photograph of a hemorrhagic yellowish-white pheochromocytoma. Remnant of normal adrenal gland can be seen This tumor appeared in a patient with von Recklinghausen's disease (W U neg 50-2610)

Fig 532 Photomicrograph of a functioning pheochromocytoma. Note delicate vessels surrounding groups of cells and lack of mitotic activity The intense granularity of the cytoplasm is due to a positive reaction to chromate (×600) (W U neg 58-4083)

malignant but are bilateral in about 30 per cent of the cases. Occasionally they are associated with neurofibromatosis (Rosenthal) or occur within the same family. They may arise from Zuckerkandl's gland. Tumors which are possibly active have been reported within the mediastinum (Overholt). Grossly these tumors vary in size from a few millimeters to 2,000 grams. They are invariably encapsulated, are usually soft, and on section are yellowish white to reddish brown (Fig 531). They are extremely well vascularized. The larger tumors often have areas of necrosis, hemorrhage and cyst formation. The adrenal usually is compressed or incorporated within the tumor. More than one tumor may be present. Ganem reported tumor in the adrenal and retroperitoneal space. Cragg reported concurrent tumors of the left carotid body and both Zuckerkandl bodies. Microscopically tumor cells vary considerably in size and shape and have a finely granular and basophilic or eosinophilic cytoplasm. The nuclei are usually round or oval with prominent neucleoli (Fig 532). Individual cells often are suggestive of ganglion cells. The tumor if immersed in dichromate solution takes on a characteristic dark brown appearance.

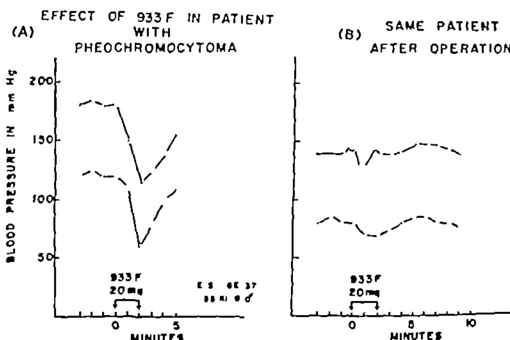


Fig 533 —Chart to demonstrate the diagnostic value of the drug 933-F in a patient with pheochromocytoma. (W U neg 50-1569) (From Calkins E. J Clin. Endocrinol. 10: 1 1950)

Assays of adrenal contents of individual pheochromocytomas have been reported as high as 682 mg per 100 grams of tissue (Roth). Elevated basal metabolic rate as well as diabetic type sugar tolerance curves may indicate a pheochromocytoma. Duncan suggested that when diabetes mellitus, hypermetabolism and hypertension are encountered together, pheochromocytoma should be considered. Piperidylmethyl Benzodioxane (933 F) and Regitine (phentolamine methanesulfonate) compete with epinephrine and allied compounds for an epinephrine specific receptor. If those drugs are given to a patient with pheochromo-

cytoma a prominent drop in the blood pressure usually follows (Fig 533) In these cases the hypertension may be due to the direct effect of the pressor substance on the arteriolar bed and the myocardium In rare instances there is no response it is thought by Calkins that the pheochromocytoma may produce hypertension indirectly by stimulation of the pituitary and adrenal The urine can be assayed for catechol amines If these substances are present contraction of strips of rabbit aorta can be demonstrated The contraction can be abolished by pretreating the aortic strip by Dibenamine indicating the specificity of the test (Helmer) The treatment is excision Colston uses an upper abdominal transverse incision

The clinical signs and symptoms of this tumor or of the hormonally active pheochromocytoma are the same as those produced by the injection of large amounts of epinephrine Of 176 pheochromocytomas reviewed by Calkins only 40 were shown to be hormonally active Hypertensive attacks are usually intermittent but at times may be sustained particularly in children (Moore) They may be brought on by massaging the area of the tumor frequently at operation crises occur through handling Histamine injection is probably contraindicated as a diagnostic procedure because of the severity of the hypertension likely to occur following its use

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Chapter 15

GENITOURINARY TRACT

KIDNEY

INTRODUCTION

Partial or complete nephrectomy is indicated for a variety of infectious degenerative and neoplastic conditions. Before the kidney is opened careful search should be made for aberrant vessels and any ureteral constriction particularly at

the ureteropelvic junction. The gross examination of renal specimens containing neoplasms must determine by dissection of hilar vessels whether or not a tumor is growing within the vein lumina. Any narrowing or plaques within the renal artery should be recorded. The capsule of the kidney should be stripped and the kidney transected to expose the entire renal pelvis. The character of stones should be studied; roentgenograms may be helpful. In a group of patients with nephrolithiasis and hypercalcuria studied by Goldman, 7 per cent had hyperparathyroidism. Their tubular reabsorption of phosphate was uniformly subnormal. This was diagnostic of hyperparathyroidism in patients with minimal hypercalcuria and normal serum phosphate levels. Sections for microscopic study should be large enough to include the cortex, medulla, and pelvis; multiple sections 5 mm. thick of the entire specimen should be studied grossly so that small unsuspected lesions will not be overlooked.

The vascular anatomy of the kidney allows emboli to reach the glomeruli either via interlobular arteries or through arteries passing directly to the afferent arterioles. The lymphatic vessels have recently been described by Rawson as follows:

> Two separate systems of channels were demonstrated: one begins as tiny blind-ending vessels close to Bowman's capsule; these enlarge to form nets about the cortical blood vessels, accompany the interlobular vessels toward the hilus, wind around the arcuate and interlobular vessels and leave the kidney at the hilus. The other system begins blindly as a network beneath the mucosa of the papillae; the channels enlarge and ascend through the medulla parallel to the blood vessels and empty into the larger lymphatic channels that surround the arcuate arteries and veins. No lymphatics are demonstrable in the glomeruli, about the afferent or efferent arterioles or about the intertubular capillaries.

EXFOLIATIVE CYTOLOGY AND BIOPSY

The material submitted for study usually consists of urine obtained at cystoscopy or bladder washings. Catheterized urine is superior to voided specimens since the cells appear better preserved. An equal amount of 95 per cent alcohol is added to the urine before centrifugation to counteract cellular degeneration. If the urine is grossly bloody, 10 per cent formalin instead of alcohol is added. The material is spun for fifteen minutes at medium speed, the supernatant discarded, and the sediment placed on slides and smeared. While the slides are still moist, they are immersed in fixative (equal parts 95 per cent alcohol and ether). They are stained by the Papanicolaou procedure.

Fremont-Smith was able to diagnose correctly only half of a small group of cases. He found a false positive in one out of ten instances (Figs. 534 and 535). Tumor cells from the kidney are probably either adenocarcinoma or transitional cell carcinoma. If the transitional cells are undifferentiated, carcinoma may be recognized. If normal appearing transitional cells are found, there may be either no tumor or a well-differentiated transitional-cell cancer.

In patients with keratinizing squamous carcinoma arising from renal pelvis or ureter, carcinoma cells can be recognized. These lesions, however, are rare.

Because adenocarcinomas usually contain large amounts of fat Daut has suggested the staining of cells found in the urine for fat in order to distinguish between the transitional cell carcinoma and the adenocarcinoma Focal hyperplasia of renal tubular epithelium may produce cells in the urine which are mistaken for car cinoma (Fig 536) As carcinoma arises from the renal cortex no tumor cells are

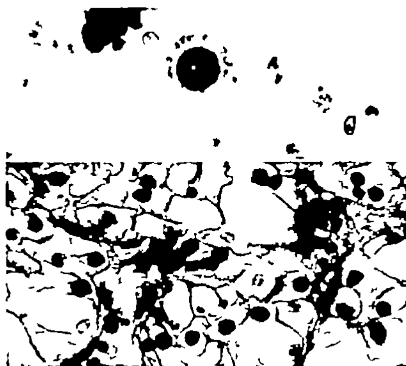


Fig 534 —Photomicrograph of a single tumor cell with a prominent nucleus felt to be characteristic of carcinoma of the kidney (600) (W U neg 49 5317)

Fig 535 —*Photomicrograph of section of carcinoma of the kidney from same tumor* Note prominence of nuclei (400) (W U neg 49 5319)

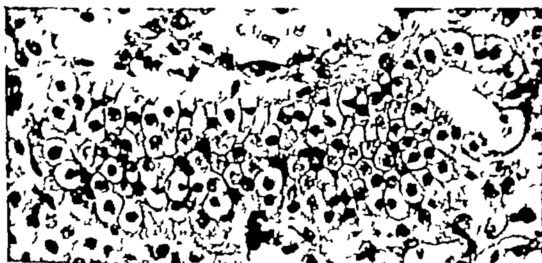


Fig 536 —Photomicrograph of focal hyperplasia of renal tubules. The cells are large with clear cytoplasm and prominent nuclei. The patient, a middle aged woman had hema turia, a questionable pyelographic abnormality cells found in the urine were indistinguishable from those seen in carcinoma The removed kidney showed only focal hyperplasia of renal tubules. (×440) (W U neg 52 2479)

exfoliated except late in its evolution. Wilms' tumor probably will never be diagnosed by cytology because only rarely are tumor cells found in the urinary stream. We have concluded that cytology is unreliable for diagnosing adenocarcinoma of the kidney and for well-differentiated tumors of the renal pelvis and ureter. Its use is restricted to the few undifferentiated transitional and keratinizing squamous carcinomas of the renal pelvis and ureter.



Fig. 537.—Photomicrographs of two needle biopsies of the kidney. *A*, Subacute glomerulonephritis with epithelial crescents and capsular adhesions. *B*, Amyloid disease with replacement of the glomerulus with amyloid. (×300.) (W.U. negs. 55-6044 and 55-6045.)

Incisional and Needle Biopsy

Incisional biopsy at the time of operation is rarely done at our institution. If the lesion is cancer, implantation is a distinct risk. If a cystic lesion is needled

and contains clear fluid it is not a neoplasm We have performed an increasing number of needle biopsies for nonneoplastic diseases of the kidney This type of biopsy may be complicated by transient hematuria in more than 100 reported cases of renal biopsy only one death was attributable to the procedure (Ogilvie) It is useful in the diagnosis of the nephrotic syndrome diabetic nephropathy, amyloidosis and the differentiation of chronic nephritis and acute anuria. It has been shown that ACTH therapy is effective in the nephrotic syndrome in cases showing only minimal histologic changes in the glomeruli (Bjorneboe) In acute anuria the nature of the biopsy findings will enable the clinician to select patients for dialysis (Fig 537) Muehrcke has shown that the biopsied material may be useful for bacteriologic study The fresh tissue obtained can be studied by histochemistry and electron microscopy Needle biopsy is contraindicated if the patient has a bleeding tendency a single functional kidney severe calcific atherosclerosis perinephric abscess pyonephrosis or malignant neoplasm

CONGENITAL DEFECTS

Congenital defects of the kidney are important surgical problems. Polycystic disease usually a bilateral entity becomes noteworthy only when secondary infection stones or other complications appear Occasionally a congenital defect results in removal of the kidney because of concomitant pyelonephritis hydronephrosis, or calculus these complications account for 90 per cent of the renal complications secondary to congenital abnormalities such as hyperplastic, polycystic, and horseshoe kidneys and those with ectopic or aberrant vessels (Smith) Any type of neoplasm also can arise in abnormal kidneys An adenocarcinoma (Ladewig) and Wilms tumor (McGinn) have been reported in horseshoe kidneys. Various types of specific infections such as tuberculosis may occur in abnormal kidneys.

A dysplastic kidney occurring in a child is difficult to differentiate from congenital polycystic disease although the presence of large cysts in a child with congenital cystic disease is unlikely the cortex and medulla at this age usually contain only multiple small cysts (Fig 538) In renal dysplasia there are primitive ducts tubules and often cartilage It is thought that the abnormal ductules have their origin in abnormal ureteric development with absence of a union between the ureteric and metanephric parts of the metanephron Such dysplastic areas are prone to the development of pyelonephritis (Ericsson) Microscopically both lesions are similar they show diminution in number of nephrons embryonic connective tissue and occasionally small islands of cartilage (Fig 539) It is important to make the differentiation however because the prognosis of patients with congenital polycystic disease is undoubtedly worse than that of patients with cystic dysplastic kidney

Megaloureter

Megaloureter may be associated with Hirschprung's disease. It is possible that its etiology may be related to diminution in the parasympathetic ganglion cells (Swenson) Ganglion cells are not present within the muscle layers of the ureter

but are present on the external surface of the bladder in the region of the intra mural portion of the ureter

In sickle cell disease the patient may be bleeding from one kidney and pyelography may show a filling defect. A diagnosis of cancer of the kidney may then





Fig 538.—Gross photograph of dysplastic kidney in a child 17 days old. The opposite kidney appeared normal by pyelogram. (W U neg 49 5299)

Fig 539—Photomicrograph of the kidney shown in Fi a embryonic-like connective tissue and tubules. (×250) (W U neg 50-329)

be made and the changes found on pathologic ... be secondary to sickle cell disease. G ... ys show little, ... is an invariable presence of ... cytes. Th...

into the peritubular areas or into the tubules and severe stasis in peritubular capillaries in the cortex and medulla (Fig 510) No thrombi are present (Mostofi)

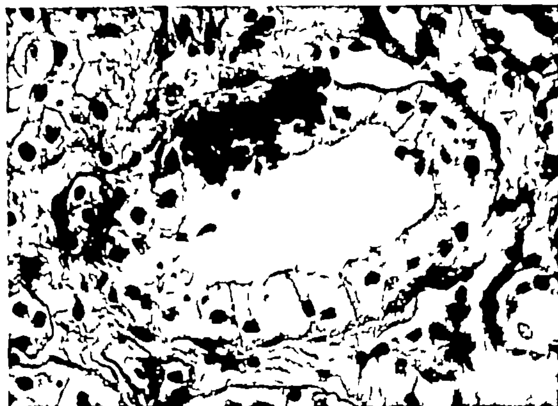


Fig 540 —Photomicrograph of a tubule in sickle cell disease There is extravasation of blood into the tubule (×400) (AFIP 54 17307) (Contributed by Lt Col. Colin F Vorder Bruegge)

SINGLE CYSTS

The single cyst of the kidney may enlarge sufficiently to encroach on other structures and cause symptoms. The cause of these cysts is unknown but may in some way relate to interference with urinary drainage and local blood supply (Harpster Heplar) Grossly these large cysts should not be confused with the common small subcapsular cyst so often found at autopsy in association with arteriosclerotic disease These cysts usually are filled with clear fluid, have a smooth external surface may be attached by adhesions to other organs but seldom communicate with the calyces or the renal pelvis (Figs. 541 and 542) The fibrous wall of the cyst usually is formed by the renal capsule and contains tubular remnants Microscopically there may be a flat epithelial lining

In 249 kidney cysts collected by Heplar 212 were serous and 37 were hemorrhagic (Fig 543) Necrosis and calcification can occur in a carcinoma with secondary cyst formation (Figs 544 and 545) Eighteen of the 37 were associated with other lesions 12 were malignant neoplasms. Needle aspiration of the single cyst may at times be diagnostic pyelograms merely show a mass which may or may not be carcinoma. The treatment of these cysts is removal by partial resection of the kidney

Fig 541—Roentgenogram with retrograde pyelography Note distortion of superior calyx of left kidney The patient had hematuria and a differential diagnosis between cyst and tumor could not be made. (W U neg. 49-7135)

Fig 542.—Gross photograph of the kidney shown in Fig 541 after removal, demonstrating a small cyst rather than neoplasm. (W U neg 49-7079)



Fig 543—Single large hemorrhagic cyst of the lower pole of the kidney Carcinoma was present within it. Secondary calcification can occur in such lesions. (W U neg. 51 199)





Fig 544 —Retrograde pyelogram demonstrating calcified cystic mass in upper pole of kidney (W U neg 49-6740)

Fig 545 —Gross photograph demonstrating calcified cystic mass which contains small focus of carcinoma. Apparently hemorrhage necrosis and calcification occurred in a circumscribed adenocarcinoma of the kidney (W U neg 49 5682.)

POLYCYSTIC KIDNEY

Congenital polycystic renal disease is hereditary It may be discovered shortly after birth but is more likely to be diagnosed after the patient is 30 years of age. In a large series reported by Bell only two cases were in patients between the ages of 1 month and 25 years Because the polycystic condition usually is bilateral, it is not amenable to surgery Complications in this type of kidney are common however and include pyelonephritis lithiasis tuberculosis and neoplasm. Rarely this condition may be predominantly unilateral in either adult or child. Nine of 150 cases collected by Sieber and 11 of 64 studied by Bell were unilateral Single large cystic kidneys in children are often impossible to differentiate clinically from Wilms tumor

Grossly the kidney retains its normal shape but may show all degrees of cystic degeneration ranging from a few isolated cysts to a kidney completely honeycombed (Fig 546) In infancy the kidneys are usually riddled with fairly uniform small cysts In adults these cysts are larger and vary greatly in size. In advanced disease the cysts involve both the cortex and medulla. The cysts frequently communicate with the calyces in adults but rarely in children. The amount of normal parenchyma varies widely The degree of cystic change is not always the same in both kidneys.

The microscopic appearance of the polycystic kidney varies. The glomeruli in the subcapsular areas frequently appear normal In the young child the connective tissue appears embryonic, and there are numerous cystic spaces which can be demonstrated by serial section to have no outlet

In the embryo the ureter and the wolffian duct fuse with the metanephric blastema. The tubules which form the collecting tubules divide and subdivide repeatedly and finally connect with the convoluted tubules. Ribbert s theory (1900) is that there is no union in polycystic disease. Kampmeier feels that there is a persistence



Fig 546—Extensive polycystic disease of the kidney in an adult There is practically no functioning parenchyma. (W U neg 48-3799)

of fetal cysts formed from the first two generations of the detached convoluted tubules. Norris believes after careful study by serial section of four cases of congenital polycystic disease of the kidney that for a long period of fetal life development of the kidneys is normal. Then focal cystic dilatation of uriniferous tubules and collecting ducts occurs.

Lambert s study of polycystic disease of the kidney demonstrated that in the child there is no communication between kidney and pelvis and therefore no function in the cystic nephrons but in the adult, nephrons do communicate with the pelvis. The cystic dilatation occurs at any point in the nephron Lambert injected inulin into the peritoneal cavity of a dying patient and found inulin within the tubules at autopsy This finding showed that the nephron functioned and that inulin had passed through the glomeruli. He also demonstrated that the creatinine and urea levels in the cystic tubules were much higher than in the blood. This finding indicated water absorption by the cysts These well-documented experiments demonstrate function of cystic nephrons in polycystic kidneys of adults.

This functional activity may account for the relatively long life of many patients with extensive cyst formation

The prognosis following surgical removal of a polycystic kidney is obviously dependent on the function of the remaining kidney If there is decrease of renal function demonstrated by retention tests before operation the prognosis is poor Of 31 patients reported by Walters 18 were living from one to nineteen years after operation The youngest patient operated on at the age of 21 months had been living over fourteen years at the time of the report

HYDRONEPHROSIS

Hydronephrosis or dilatation of the renal pelvis follows partial block of urinary outflow Complete block (ligature) produces acute renal atrophy without significant ureteropelvic dilatation Partial block can occur at any level in the urinary tract the most common is nodular hypertrophy and hyperplasia of the prostate Numerous malignant lesions may partially block one or both ureters the most frequent being carcinoma of the prostate bladder or cervix Rarely carcinoma of the ovary or rectum and more rarely leiomyoma of the uterus cause hydronephrosis. Aberrant vessels at the juncture of the ureter and the pelvis may cause obstruction These arteries may arise from the aorta or independently from the ovarian sper matic, or iliac arteries An aberrant vessel is often thought to be the cause of hydronephrosis in children White reported 30 such cases. Ostling feels that congenital ureteropelvic fixation may cause stricture

Grossly the hydronephrotic kidney may show any degree of dilatation. On section the dilated kidney may contain 300 to 500 c c. of urine. The calyces are blunted and the cortex is narrowed (Figs 547 and 548) When the renal collecting system is sufficiently obstructed so that it is not visualized by pyelography renal function (indicated by subsequent dye excretion) likely will return if the obstruction is removed or the urinary stream is diverted before complete parenchymal destruction occurs

Microscopically in early hydronephrosis the tubules are slightly dilated, a change which is replaced by atrophy in older more advanced hydronephrosis. The glomeruli appear normal The section shows atrophied tubules and glomeruli apparently more numerous than normal because of parenchymal compression and atrophy The hydronephrosis in kidneys removed surgically is usually advanced In the advanced lesion the tubules become extremely atrophic, the glomeruli become hyalinized and sometimes difficult to recognize, and the entire cortex of the kidney may shrink to only a few millimeters. In this situation infection frequently exists and hydronephrosis is complicated by pyelonephritis.

HYPERTENSION

A kidney altered by various pathologic processes may cause hypertension its removal may relieve the hypertension It has been difficult, however to accurately select those patients who will benefit from nephrectomy Although the blood pressure frequently falls after removal of the diseased kidney it may soon return to the preoperative level It has been suggested that at least a year should



Fig 547.—Extreme hydronephrosis with nonfunctioning kidney due to congenital uretero-pelvic obstruction. (W U neg 50-3275)

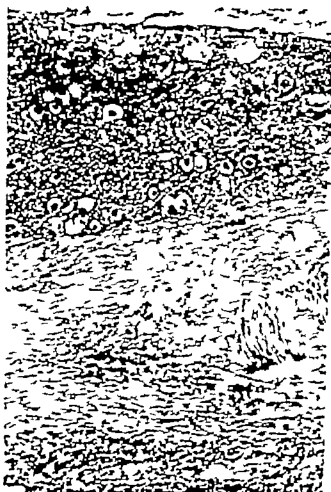


Fig. 548.—Photomicrograph of entire width of kidney Note compression of the cortex to a small band made up of hyalinized glomeruli, fibrous tissue and obliterated tubules The pelvis shows focal hyperplasia of smooth muscle and slight chronic inflammation (×100) (W U neg 49-6718)

lapse before results of the operation are evaluated In 575 patients who had nephrectomies for hypertension 26 per cent were improved In the evaluation of these patients the blood pressure was reduced to at least 140/90 for a minimum period of one year (Smith)

Goldblatt demonstrated in dogs that prolonged hypertension could be produced by reduction of the arterial blood supply to one kidney The combination of renin a proteolytic enzyme elaborated by the ischemic kidney with plasma globulin to produce an active pressor polypeptide is postulated as the cause of the hypertension Howard felt that renal infarction would produce hypertension if the infarct were surrounded by a zone of tubular atrophy indicative of vascular insufficiency Burns reviewed his patients with hypertension and pyelonephritis and found that if the hypertension had been relieved by nephrectomy severe sclerosis of the renal artery was present The kidney usually is removed in the patient with unilateral chronic pyelonephritis in these instances the kidney is small and severe atrophy is present If prominent arteriolar disease also is found the chances are high that it will be present in the opposite kidney and that the hypertension will not be relieved permanently An aneurysm of the renal artery is a rarer cause of hypertension occurring most frequently in people between 40 and 60 years of age Abeshouse could find only 115 reported cases This aneurysm most frequently appears to be poststenotic occurring just beyond an arteriosclerotic plaque The following typical case illustrates the difficulty of diagnosis

A 26-year-old woman entered the hospital with a history of hypertension for thirteen years. Intravenous pyelograms and urinary function were normal. Differential sodium studies of the kidneys did not help determine a unilateral renal abnormality Aortography demonstrated renal artery aneurysm. The kidney was removed it weighed 150 grams and showed no evidence of pyelonephritis or infarction. The lumen of the renal artery was narrowed by an atheromatous plaque The branch of the artery to the upper pole of the kidney was normal but the lower pole branch showed aneurysmal dilatation and thinning Microscopic examination of the kidney revealed no significant abnormalities. The wall of the aneurysm was thin and contained very little smooth muscle (Fig 549)

We believe this patient has a very favorable prognosis since the kidney was normal and showed no arteriolar disease This case history illustrates diagnostic value of aortography (Edholm)

Hypertension also may be caused by partial infarction of the kidney (total infarction does not produce hypertension) Arterial thrombosis with segmental renal infarction may follow emboli hemorrhage into a localized arteriosclerotic plaque and rarely trauma to the vessels The following case illustrates traumatic infarction

A 62 year-old man was in an automobile accident and sustained several fractures which healed without incident He had no renal symptoms of hypertension at this time Two months later he developed severe headaches Blood pressure was found to be 240/130 Vascular disease was noted in his eyegrounds Brain tumor was suspected Ventriculograms were normal. Albumin and red blood cells were found in the urine Retrograde pyelography showed a slightly atrophic nonfunctioning left kidney a diagnosis of infarction was made Nephrectomy was performed At operation (three months after the accident) occlusion of the left renal artery produced severe hypertension The patient recovered uneventfully and has remained normotensive The eyeground changes disappeared. Examination of the kidney

showed infarction of about one half its substance there was thrombosis of both the renal artery and vein. The histologic age of the thrombi was compatible with the time of the accident (Fig 550)

Nephrectomy has its greatest value in those hypertensive patients in whom the disease has been of short duration, where pathologic examination demonstrates some localized abnormality of the renal artery, and where these changes are accompanied by either a normal kidney or a kidney in which there is evidence of localized renal ischemia without arteriolar disease.

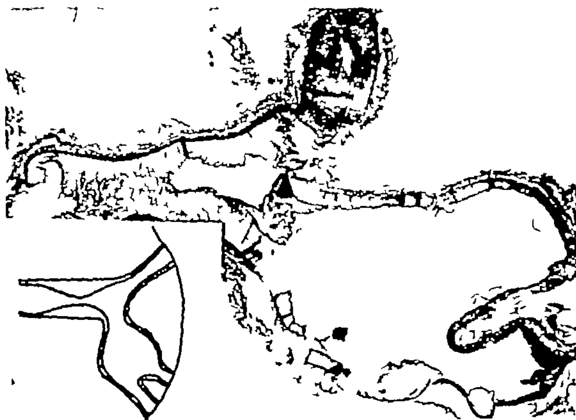


Fig. 549 —Photomicrograph of narrowing of the renal artery with aneurysmal dilatation and thinning of the branch to the lower pole. The inset diagrams this abnormality (Low power) (W U neg 58-805)

PYELONEPHRITIS

Pyelonephritis may be acute or chronic There are three peaks of incidence infancy and childhood, the childbearing age and in the aged (Keefer) When the process is unilateral it is a surgical problem When it is acute, there may be other complications such as perirenal infection

Chronic pyelonephritis is the commonest disease of the kidney for which nephrectomy is done. It is also the commonest type of renal disease found at autopsy (Beeson) Whenever it occurs it is invariably associated with some degree of block This causative factor has been well demonstrated experimentally A ureter was partially blocked in a rabbit and bacteria were introduced into the blood stream Infection then localized in the blocked kidney but not in the other kidney When the block was removed, the infection cleared (Mallory) In human

beings the same sequence occurs In children the block is often on a congenital basis In pregnant women the ureters are partially blocked or distorted by the enlarged uterus In the older age groups there are multiple causes of obstruction in males cancer of the prostate and nodular hypertrophy and hyperplasia occur in females cancer of the cervix is often a cause

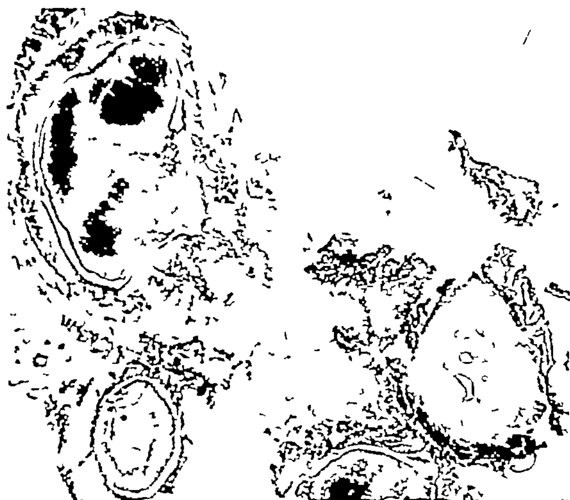


Fig 550—Photomicrograph of thrombosis of branches of the renal artery and vein. These thrombi are of three months duration. (Low power) (W U neg 58-806.)

Grossly the kidney in acute pyelonephritis is larger than normal and often has an adherent capsule If the pyelonephritis is recent there may be small yellow abscesses observed beneath the stripped capsule On section there are numerous small abscesses in the cortex and prominent linear bands in the medulla indicating pus in the tubules (Fig 551) The pelvis is infected.

Microscopically diffuse inflammation may be seen in the pelvis and between the tubules (Fig 552) At times there are confluent abscesses. Various renal areas may show varying stages of infection

Grossly the kidney in chronic pyelonephritis is reduced in size and may be as small as 60 to 80 grams. The capsule strips with great difficulty and there are flat irregular wedged scars on the surface Infrequently the gross appearance will show no wedge shaped scars but will be greatly reduced in size and have an external surface which is finely granular This type of gross alteration may also

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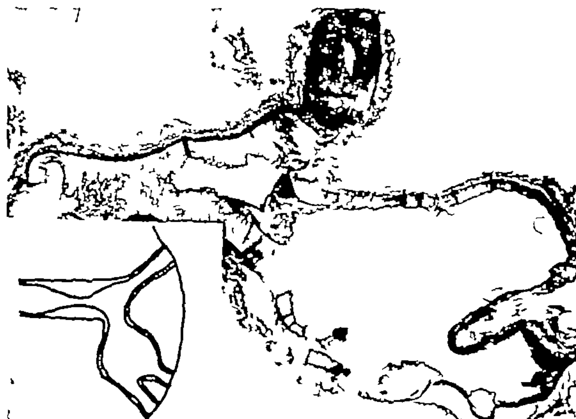


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be observed in experimental pyelonephritis. Usually there is some hydronephrosis, and stones may or may not be present. Ureteritis cystica occasionally occurs in the ureter. The cortex is irregular and the calyces are blunted. It is important to note whether there is partial atheromatous occlusion of the renal artery. The





Fig. 551. Surgical specimen of kidney with slight hydronephrosis and acute pyelonephritis. Note linear streaks in the medulla due to pus within the tubules. (W U neg 49 5678.)

Fig. 552.—Photomicrograph of the kidney in Fig. 551 shows masses of polymorphonuclear leukocytes within the tubules. Note interstitial inflammation. (× 250.) (W U neg 50-378.)

latter determines whether the nephrectomy will reduce possible existing hypertension or not. Microscopically there are focal areas of hyalinized glomeruli, atrophic tubules, and colloid casts. Arteriolar disease may or may not be present. Renal papillary necrosis most frequently occurs in diabetics or in patients with obstructive uropathy There are infarctlike zones of necrosis of the papillae extending upward into the pyramids. These necrotic papillae may be passed and identified in the urinary sediment. Pyelograms show ragged calyces, ring shadows, and clubbing (Garrett)

There is another form of chronic pyelonephritis usually associated with lithiasis which we have designated as chronic pyelonephritis with xanthogranulomatous change (Fig 553) The kidneys in this condition show extreme enlargement with hydronephrosis and ureteral obstruction On section there are yellow lobulated masses replacing the architecture of the kidney and extending into the pelvis and perirenal fat. Microscopically granulomas are prominent with multinucleated giant cells and foam cells This condition occurred three times among 222 kidneys removed for various inflammatory conditions (Ghosh)

PYELITIS AND URETERITIS CYSTICA

Hinman demonstrated that pyelitis and ureteritis cystica are the result of chronic inflammation of variable etiology He believes that their development is due to chronic inflammation of the mucous membrane followed by downward proliferation of the surface epithelium These buds of epithelium become pinched off possibly by the upgrowing connective tissue and form epithelial cell nests. Degeneration occurs centrally and a cystic structure forms (Fig 554) This lesion may be diagnosed by identifying peculiar mottled like bubble defects in the ureterogram

LIPOMATOSIS

Lipomatosis must be differentiated from a true lipoma of the kidney There is fatty replacement of normal tissue and an increase of fat in the hilus of the kidney This replacement occurs whenever there is atrophy or arteriosclerosis of the kidney It is present quite frequently in association with chronic pyelonephritis and renal stone (Hamm Young) It may be confused pyelographically with carcinoma (Fig 555)

Grossly there is diffuse fatty replacement in the region of the hilum and the remaining kidney is atrophic (Fig 556) Microscopically there are no features of interest. Clinically extensive lipomatosis with stone may simulate renal neoplasm because of the filling defect usually seen pyelographically

RENAL LITHIASIS

Primary renal stones are defined as those which occur in the absence of renal abnormality persistent infection, or metabolic disease. Practically all renal stones develop within the renal pelvis often in the major or minor calyx. Randall

Fig. [illegible] cystica [illegible]

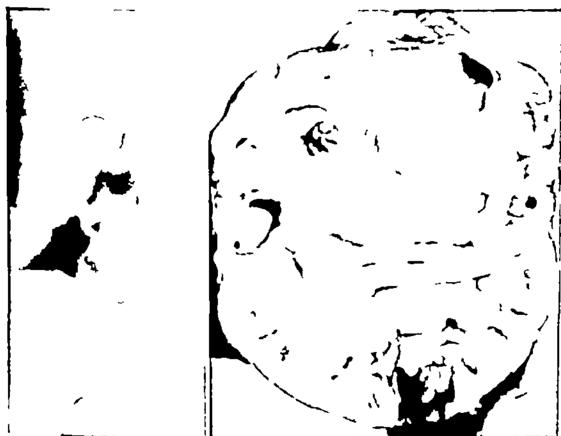


Fig. 555. Retrograde pyelogram which illustrates pyelographic deformity of unknown etiology. Malignant tumor was seriously considered. (W.U. neg. 18-3835.)

Fig. 556. Cross photograph of the kidney shown in Fig. 555 with extensive lipomatosis and stone formation without evidence of neoplasm. (W.U. neg. 18-379[illegible].)

latter determines whether the nephrectomy will reduce possible existing hypertension or not. Microscopically there are focal areas of hyalinized glomeruli atrophic tubules, and colloid casts. Arteriolar disease may or may not be present. Renal papillary necrosis most frequently occurs in diabetics or in patients with obstructive uropathy There are infarctlike zones of necrosis of the papillae extending upward into the pyramids These necrotic papillae may be passed and identified in the urinary sediment. Pyelograms show ragged calyces, ring shadows, and clubbing (Garrett)

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Fig 554 — Gross photograph of kidney with hydronephrosis and prominent ureteritis cystica. (W U neg 53-1346)



Fig 555 Retrograde pyelogram which demonstrates pyelographic deformity of unknown etiology Malignant tumor was seriously considered. (W U neg 48 3845)

Fig 556 Gross photograph of the kidney shown in Fig 555 with extensive lipomatosis and stone formation without evidence of neoplasm. (W U neg 48-3792)

studied 1 154 pairs of kidneys 227 (19 6 per cent) showed calcium salt deposition in one or more renal papillae 65 showed a renal calculus attached to a renal papilla. These calculi were subepithelial and represented a plaque of calcium salt in the interstitial tissue the first deposition of calcium salts was in the basement membrane of the walls of the collecting tubules. A primary renal calculus obtains



Fig 557 —Gross photograph of kidney with staghorn calculi, hydronephrosis chronic pyelonephritis and almost complete obstruction of the ureter at the ureteropelvic junction. (V U neg 50-3971)

its freedom by tearing away the plaque It is interesting that the chemical composition of the calculus may consist of two entirely different substances the one which is deposited secondarily depends upon the saturation of chemicals in the urinary stream. Calculi arise from pathogenic conditions within the renal papillae and damage to the collecting tubules and the supporting interstitial tissue follows With attempted repair calcium salt deposition is either intra or extra tubular Interstitial deposition of calcium salt is much slower than its intra tubular deposition Interstitially calcium carbonate and calcium phosphate may be identified Ulceration of the surface of the papilla acts as the nidus upon which urinary salts crystallize Intratubular calcium phosphate calculi may be associated with secondary infarction of the papillae Vitamin A deficiency may damage the renal tubule epithelium sufficiently to cause secondary calcium salt deposition In hyperparathyroidism intratubular type of damage occurs

Randall s theory explains the origin of calculi which have arisen on papillae Anderson investigated microscopic calculi in the kidney and demonstrated that phagocytes outside of the tubules absorb blue black material into their cytoplasm Carr has a new theory related to the lymphatics He believes that the formation of stones is facilitated when the lymphatic drainage of the kidney is either over loaded or blocked He thinks that the obstructing point is where the lymph duct leaves the kidney substance and enters the renal sinus at the calyceal fornices If growth of stones occurs at this point there will be necrosis of the membrane separating the concretion from the lumen of the calyx allowing seepage of urine into the area of calcification This facilitates further growth of the stone by deposition of urinary salts. If there is reversal of lymphatic flow microliths may flow backward and collect at the tip of the renal papillae forming a Randall plaque Carr emphasized that these deposits first occur outside the tubules. A stone forming in a calyx indicates that the lymphatic duct from the lobule has either been obstructed or overloaded Therefore partial nephrectomy for stone should include a whole segment of kidney otherwise further stones may form in the diseased segment Carr s attractive theory was supported by the use of defraction x ray analysis.

Renal stones may be recognized not only by their gross appearance but also by their radiologic changes (Fig 557) With alkaline urine the stones contain calcium ammonium phosphorus, and magnesium In hyperparathyroidism the stones are made up of calcium and phosphorus but if there is infection the stones become coated with magnesium and ammonium phosphates (Albright) With an acid urine calcium oxylate forms stones with a crystalline structure radiating to a central point Phosphorus stones grow in size by concentric layers

TUBERCULOSIS

Practically all renal tuberculosis is hematogenous in origin The infection usually originates from foci in the lung but in a few instances it may arise from bone lesions. Rarely tuberculous renal infection may occur secondary to paravertebral abscess. Tuberculous lesions appear initially in the cortex of the kidney usually within the glomeruli at this stage the infection must be bilateral



Fig 558.—Intravenous pyelogram showing marked abnormalities of the right kidney due to tuberculosis. (W U neg 49-6736.)

Fig 559 —Gross photograph of the kidney shown in Fig 558 Note extensive destruction of the kidney by tuberculosis with the formation of permanent cavities communicating with the pelvis. Note involvement of the ureter Such a kidney does not heal. (W U neg 47 3510)

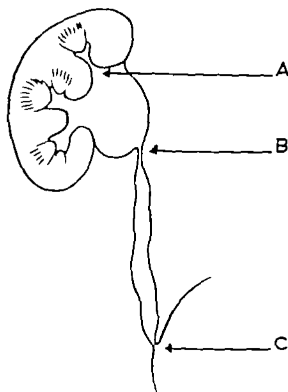


Fig 560 —Danger sites for the fibrous of 'healing are the neck of a calyx *(A)* the ureteropelvic junction *(B)* and the ureterovesical region *(C)* (From Hanley H G Brit J Surg 45 10 1957)

(Medlar) The lesions either completely heal and become fibrous scars (Reichle) or more often progress in one kidney but remain stationary in the other In 56 cases of renal tuberculosis reported by Auerbach 11 showed unilateral involvement With further spread the apices of the pyramids and the wall of the calyces of the kidney are involved possibly because infected tuberculous urine is retained in the smaller crevices (Wegelin) If the urine contains tubercle bacilli then the kidney always contains a tuberculous focus which is at times difficult to identify Tuberculosis in a kidney may vary from minute areas of ulceration near the tips of the papillae to wide zones of caseation which may coalesce to form huge cavitating masses with only a shell of normal kidney (Figs 558 and 559)



Fig 561 —Gross photograph of almost complete healing of tuberculosis of the kidney There is still extreme destruction with hydronephrosis but there is no gross evidence of active disease. Fibrosis at the ureteropelvic junction is present. (W U neg 56-5140)

The change that has occurred in the pathology of tuberculosis due to the new antimicrobials has been reported by Hanley In the fibrosis of healing block can occur at the neck of the calyx, the ureteropelvic junction and the ureterovesical region (Fig 560) With isoniazid therapy caseation is absorbed vascularization of the edges of the lesion occurs with diminished fibrosis. The vascularization may facilitate the effects of isoniazid (Dick) With absorption of caseation there is rapid clinical improvement Grossly the specimen may show healing evidenced by absence of caseation and a smooth pelvis it may show also a fibrotic uretero-pelvic block (Fig 561) The incidence of tuberculosis with calculi is only 1 per cent (Greenberger)

TUMORS

Benign

The benign tumors of the kidney make up less than 5 per cent of all renal neoplasms and are of little surgical significance. The *perirenal lipoma* may become huge (Pfeiffer) grossly and microscopically it resembles lipomas elsewhere.



Fig 562—Gross photograph showing multiple areas of focal hyperplasia of renal tubules. These lesions were a bright yellow in color (W U neg 50-6340)

Fig 563—Photomicrograph of one of the small nodules shown in Fig 562 demonstrating focal hyperplasia of renal tubules (×460) (W U neg 52 2475)

Rarely *leiomyomas* of the kidney capsule may produce masses which are confused with more common renal neoplasms Zuckerman has reported one case in an infant in whom the leiomyoma was resected successfully Angiolipoleiomyoma is a rare neoplasm of the kidney composed of fat, blood vessels and smooth muscle. The blood vessels are thick walled and without elastic tissue. Although these tumors may be very large and their microscopic pattern confusing they are benign neoplasms (Tweeddale)

Small *adenomas* are quite common in the arteriosclerotic or contracted kidneys. However, whether small yellowish areas of focal renal tubular hyperplasia should be diagnosed as adenomas is questionable (Figs. 562 and 563). When these lesions become larger, they may be dignified by this designation. It is certain that from such adenomas the adenocarcinomas of the kidney arise. Adenomas of varying size are also frequently found incidentally at autopsy. The high frequency of these adenomas suggests that many carcinomas of the kidney may remain quiescent clinically for a number of years. Mintz examined 61 kidneys (58 abnormal) containing 69 small circumscribed lesions, practically all less than 5 cm in diameter: there were 17 papillary cystadenomas, 7 so-called fetal adenomas and 7 adrenal rests.



Fig. 564.—Flat plate of the abdomen in a child. Note displacement of bowel to left by a large Wilms' tumor on right. (W. U. neg. 49-6235.)

Malignant

Wilms Tumors. *Wilms' tumors of the kidney* (embryoma or adenomyosarcoma) are seen primarily in infants. Geschickter believes that they probably arise from embryonic nephrogenic tissue and represent a loss of the factors controlling normal developmental processes in the growth zone of the renal cortex in either



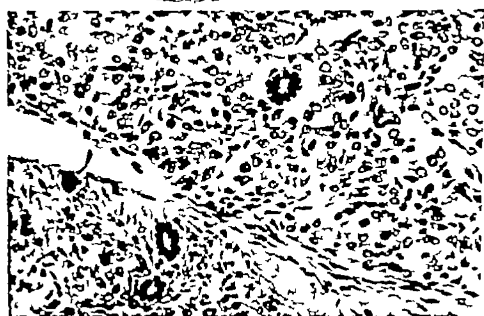


Fig 565 —Gross photograph of the Wilms tumor shown in Fig 564 The typical pseudoencapsulated appearance is seen. (W U neg 49 1689)

Fig 566 —Photomicrograph of the tumor shown in Figs 564 and 565 shows typical stroma and small tubules. Such a pattern suggests embryonic renal tissue (×400) (W U neg 50-330)

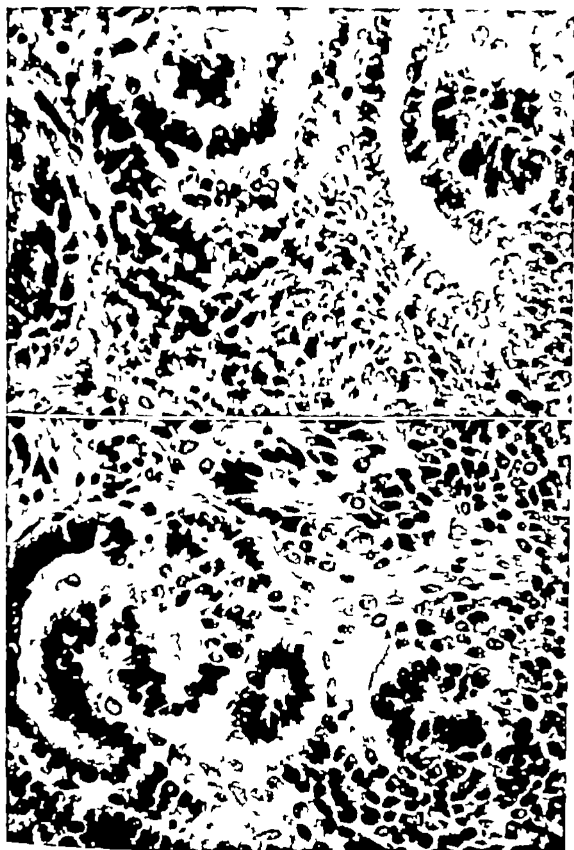


Fig 567 – *A* Between and around the ends of two collecting tubules (derivatives of the ureteric bud) is nephrogenic blastema differentiating into glomerular capsule and renal tubules *B* Structures in a nephroblastoma (Wilms tumor) that bear a striking resemblance to developing metanephric tubules in the embryonal renal blastema (×500) (AFIP 218935 213 and 218935 214) (From Lucké B and Schlumberger H G: Atlas of Tumor Pathology Section 8 Fascicle 30 Washington D C 1957 Armed Forces Institute of Pathology)



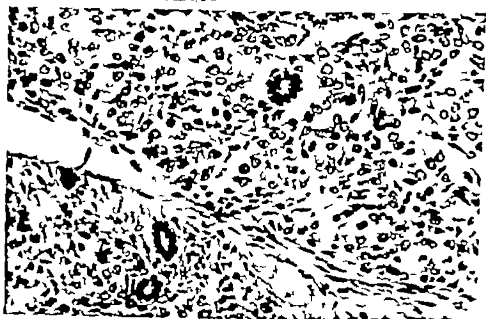


Fig. 565 —Gross photograph of the Wilms tumor shown in Fig 564 The typical pseudoencapsulated appearance is seen. (W U neg 49-1689)

Fig 566 —Photomicrograph of the tumor shown in Figs. 564 and 565 shows typical stroma and small tubules. Such a pattern suggests embryonic renal tissue. (×400) (W U neg 50-330)

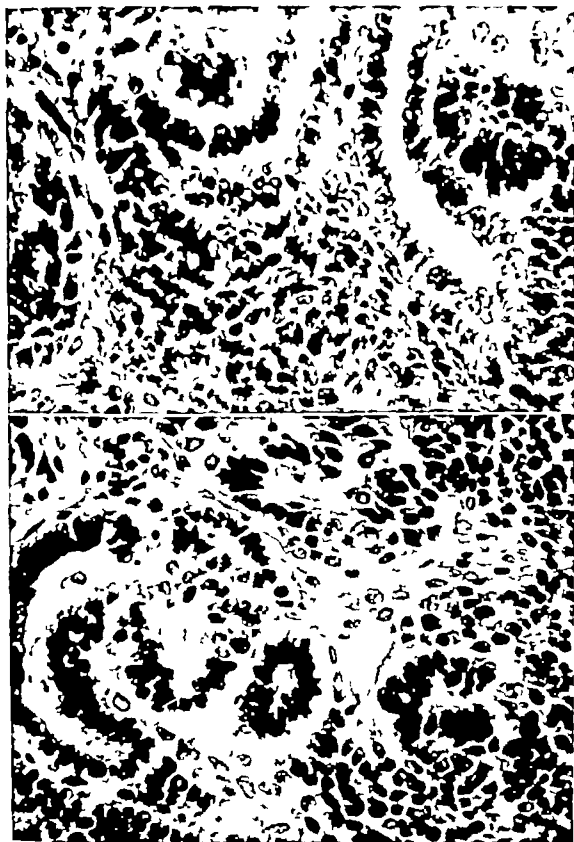


Fig 567 —*A* Between and around the ends of two collecting tubules (derivatives of the ureteric bud) is nephrogenic blastema differentiating into glomerular capsule and renal tubules *B* Structures in a nephroblastoma (Wilms tumor) that bear a striking resemblance to developing metanephric tubules in the embryonal renal blastema. (×500) (AFIP 218935 213 and 218935 214) (From Lucké B and Schlumberger H G Atlas of Tumor Pathology Section 8 Fascicle 30 Washington D C. 1957 Armed Forces Institute of Pathology)

fetal life or the first few months after birth. These tumors are usually large (over 250 grams) well delineated firm, and appear to have a definite capsule (Figs. 564-566) On section they are often grayish white sharply circumscribed and contain areas of hemorrhage. Only rarely do these tumors invade the renal pelvis or ureter hematuria is infrequent. When advanced Wilms tumor invades veins, the renal capsule, the adrenal, and later the small bowel, large bowel liver and vertebrae. Microscopically it is variable sarcomatous elements often predominate and smooth muscle and striated muscle are frequently present. Lucké and Schlumberger have demonstrated that structures in a Wilms tumor can bear a striking resemblance to developing metanephric tubules in the embryonal renal blastema (Fig 567)

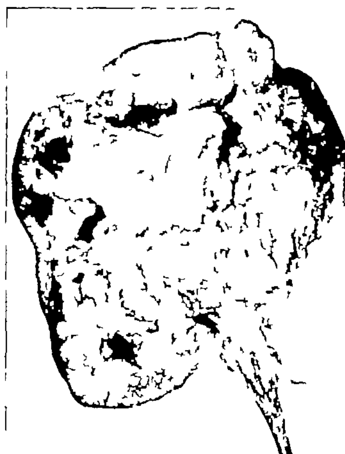


Fig 568 —Gross photograph of extensive rather undifferentiated transitional cell carcinoma involving the renal pelvis. Prominent bleeding often occurs in such tumors. (W U neg 49-6807)

The prognosis of Wilms tumor depends upon the presence of large vein involvement or penetration of the capsule The microscopic pattern is unrelated to prognosis. The first clinical indication of this tumor usually is the presence of a large mass felt by the mother when handling the child. The treatment of choice is resection The place of pre and postoperative irradiation therapy has not been clarified. The prognosis is best in patients treated during the first year of life (Abeshouse)

Transitional Cell Carcinoma — Transitional cell carcinomas of the renal pelvis are relatively rare tumors. They form soft, grayish red masses with smooth glistening surfaces and exactly resemble the transitional cell tumors of the bladder. Necrosis is uncommon (Fig 568). They often diffusely involve the entire renal pelvis and form arborescent masses which may extend down the ureter. Similar tumors rarely are primary in the ureter (Fig 569) (Whitlock). Microscopically



Fig. 569 —Gross photograph of poorly differentiated transitional cell carcinoma arising in the ureter completely blocking it and causing extreme hydronephrosis. (W U neg 48-5885)

these carcinomas form branching masses of transitional cells supported by a delicate connective tissue stroma containing many blood vessels. The extreme cellularity and vascularity of these tumors cause the profuse hematuria. Usually these tumors are well differentiated rather than poorly differentiated, although both extremes occur. Because these tumors implant along the ureter it is imperative that the ureter including its intramural portion be resected with the kidney. When the intramural portion is not resected recurrence of the tumor within this bladder segment sometimes occurs (Kimball).



Fig. 570.—Gross photograph of a kidney with hydronephrosis, chronic pyelonephritis, leukoplakia, stone formation, and keratinizing epidermoid carcinoma. (W U neg 49-4321.)



Fig 571.—The epidermoid carcinoma is clearly seen but was not suspected prior to pathologic examination. (W U neg 49-4320.)

Epidermoid Carcinoma The keratinized epidermoid carcinoma of the renal pelvis is a rare tumor associated usually with infection and renal calculi Because of infection and calculi a preoperative diagnosis is practically never made Gahagan found that the preoperative diagnosis in 106 cases was incorrect in all instances The carcinoma is found to be advanced either at operation or when the specimen is examined Cross section of the specimen usually shows extensive



Fig. 572.—Extensive leukoplakia of renal pelvis and ureter without stones. (W U negs 50 679? and 50-6791)

pyelonephritis with multiple abscesses and renal stones The necrotic and ulcerated neoplasm destroys and displaces kidney parenchyma (Figs 570 and 571) Invariably extension into surrounding tissue and involvement of distant nodes and other organs have occurred Forty-eight of 100 cases reviewed by Gahagan were associated with clinically evident stones It is thought that there is some relation between the presence of leukoplakia stones and the presence of epidermoid carcinoma. We have seen extensive leukoplakia without stones (Fig 572) The prognosis for this group of patients was hopeless

Adenocarcinoma.—Adenocarcinomas of the kidney are usually not discovered until they are sufficiently advanced to cause either a mass or hematuria These tumors often are well delineated appear in the cortex and on section are pseudoencapsulated and golden yellow in color Because of their cellularity hemorrhage, necrosis, and calcification are common (Figs. 573 and 574) These tumors often invade the renal pelvis. The presence or absence of vein invasion is the most important factor in prognosis. Microscopically they show evidence of origin from renal tubules best demonstrated in very small tumors where transition from tubules





Fig 573—Retrograde pyelogram demonstrating large tumor with smooth deformity of renal pelvis. (W U neg 49-6234)

Fig 574—Gross photograph of kidney shown in Fig. 573 demonstrating well-circumscribed hemorrhagic carcinoma of the kidney (W U neg 48-6955)

to tumor can be seen. As in normal renal tubules the tumor cells often show hyaline droplets and phagocytosis of broken-down blood pigment (Schiller) Various patterns appear the cells may be granular or clear and may show papillary formation. As Gottesman has emphasized, large sections or multiple sections usually show diverse variations in the same tumor it is not logical to make subdivisions in nomenclature, better to call it simply an adenocarcinoma of renal tubule origin. The size of these tumors is directly related to prognosis—the larger the tumor the greater the chance of spread (Bell) However exceptions to this rule do appear very small tumors may invade the renal veins and cause distant metastases. Con

versely large carcinomas of the kidney have been seen without evidence of metastasis for long periods. Adenocarcinomas metastasize through the blood stream, often to the lung. They frequently metastasize to bones particularly the pelvis and the femur where they may be mistaken for primary bone tumors. Aspiration



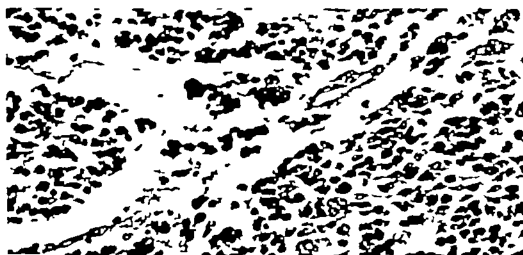


Fig 575 Gross photograph of a tumor extensively involving the pelvis and, to a slight extent, the parenchyma (W U neg 49 2147)

Fig 576 Photomicrograph of the tumor shown in Fig 575 demonstrates an undifferentiated neoplasm with cells suggesting origin from the sympathetic nervous system. (×400) (W U neg 50 331)

of these metastatic masses however may show the characteristic pattern of adenocarcinoma of the kidney. The aspirated cells usually show well-defined cellular outlines a central nucleus and foamy cytoplasm which contains sudanophilic material and a small amount of glycogen. Metastases may occur from carcinoma of the kidney to unusual locations. We have seen such metastases appear first in the gingiva, larynx and bronchus they may masquerade as primary soft tissue sarcomas.

Rare Neoplasms

We have seen a malignant tumor in an adult involving the renal pelvis and parenchyma which microscopically suggested a *tumor of the sympathetic nervous system* (Figs. 575 and 576) Glandular metaplasia of the pelvic epithelium with the formation of an *adenocarcinoma* exactly resembling those of the large bowel have been reported (Ackerman) *Liposarcomas* may originate from the fat in the region of the renal pelvis to form a hugh tumor mass *Metastatic carcinoma* can involve the kidney as a part of a disseminated process but we have seen few instances where this involvement was of surgical significance. We have also seen a *leiomyosarcoma* a *rhabdomyosarcoma* and a single instance of a well-circumscribed *mucin producing adenocarcinoma* of the cortex (*Fig 577*)

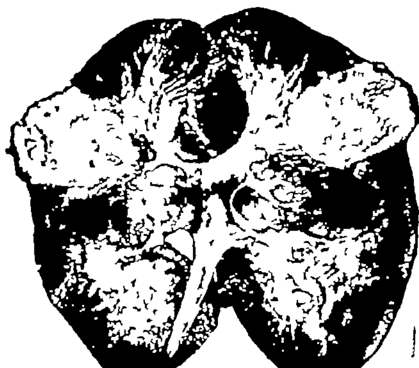


Fig 577 —Gross photograph of a well-circumscribed cortical cellular tumor mucin-producing (Courtesy Dr Franz Leidler Veterans Hospital Jefferson Barracks Mo)

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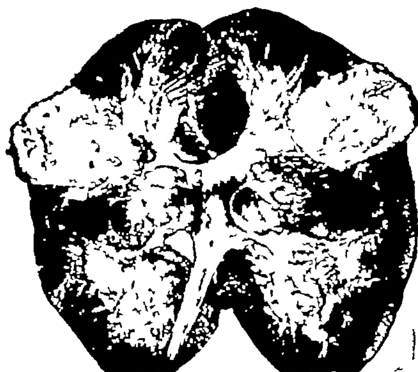


Fig 577.—Gross photograph of a well-circumscribed cortical cellular tumor mucin-producing (Courtesy Dr Franz Leidler Veterans Hospital Jefferson Barracks Mo)

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BLADDER

INTRODUCTION

Biopsy

Biopsy is indicated in all bladder tumors. The urologist should not fulgurate a papillary tumor without biopsy because it appears benign. It is true that well defined papillary tumors are often benign but exceptions occur It is therefore better practice to biopsy the tumor before fulguration. Small biopsies should be sectioned at various levels. Commonly the biopsy shows a lower grade of tumor than is found in the excised lesion. However if the tumor biopsy is undifferenti ated it is significant. Even large biopsies may not be representative of the most undifferentiated part of the tumor These undifferentiated areas are not necessarily at the base of the tumor

Exfoliative Cytology

Exfoliative cytology is of little practical value in the diagnosis of bladder tumors. In Papanicolaou s laboratory Schmidlapp reported 36 patients with histologically proved benign bladder tumors there were no malignant cells in 27



Fig 578 —Photomicrograph of chronic cystitis with prominent chronic inflammation and focal calcification. (Encrusted cystitis.) (×100) (W U neg 49-5392.)



Fig 579 —Photomicrograph of cystitis glandularis with formation of mucin-producing glands. (×225) (W U neg. 49-6717)

(1893) is still accepted There is downward projection from the inferior l of the mucosa which develops a central lumen probably by epithelial cell s tion (Patch) Cysts lined by flattened epithelium develop Secondary ce changes have been well described by Stoerk Cells assume a concentric radi pattern with basally situated nuclei within the cells are granules which stain tively with mucicarmine (Fig 579) The resulting condition is known as py ureteritis or cystitis glandularis. These changes usually occur only when ch inflammation has been present a long time The lesion may regress comp if the underlying etiologic factor is removed (Patch) Cystitis glandularis g presents an irregular mammulated appearance Chronic glandular prolifer of the bladder mucosa and the formation of polyp-like lesions may be con with carcinoma (Lowry) Beneath the polypoid masses there may be ne glandular epithelium Pund has pointed out that in the trigone glands p may resemble prostate (region of trigone derived from wolffian duct) In the of the bladder, glands present resemble large bowel

ENDOMETRIOSIS

Endometriosis is a rare condition of the bladder which has been rep approximately fifty times. The endometrioma occurs beneath intact mucos has a bluish cast This lesion undergoes cyclic change during the menstrual Forty two of 46 patients reported by Moore had had previous pelvic surge some disease of the female reproductive system. In 21 cases the endomet could be palpated in the base of the bladder Rarely intraurethral endome occurs (O Conor)

DIVERTICULUM

Diverticula of the bladder develop because of partial urinary obstruct the urethra or bladder neck Long standing increased muscular contractio quired to empty the bladder cause mucosal herniation in areas of con weakness. These areas occur in the bladder above the trigone on the po *wall the region of the urethral orifice or the site of an obliterated urachu* variably the diverticula are associated with a thickened bladder wall. The of obstruction which cause these lesions are shown in Table 25 (7 femal 229 males)

TABLE 25 TYPE OF OBSTRUCTION*

	CASES	PER CENT
Benign prostatic hypertrophy	153	66.52
Median bar	34	14 78
Contracted internal urethral orifice	18	7 82
Carcinoma of prostate	17	7.39
Stricture of the urethra	5	2.19
Congenital valves in posterior urethra	3	1.30

*From Kretschmer H. L. Surg Gynec. & Obst. 71: 491 503 1940

The communication into the bladder is usually large but may be pi in size (Spence) The wall of the diverticulum is usually made up of fibrou

without muscle Squamous metaplasia of the lining epithelium often occurs if there is associated infection. The rather frequent occurrence of carcinoma within diverticula may relate to the obstruction leukoplakia and chronic inflammation occurring in them. Diverticula may contain stones (Rathbun) Abeshouse reviewed 89 cases of malignant neoplasms occurring in diverticula there were 35 unclassified carcinomas 19 papillary carcinomas, 16 squamous carcinomas and 1 adenocarcinoma Kretschmer had 10 cases in which carcinoma was found within the diverticulum (Fig 580) These diverticula were locally resected and in nine instances the tumor locally recurred.



Fig 580 —Gross photograph of a diverticulum of the bladder which has been opened to demonstrate the carcinoma arising in it. (W U neg 50-1152)

ADENOCARCINOMA

Exstrophy of the bladder may be associated with adenocarcinoma (Figs. 581 583) Exstrophy is the absence of the anterior vesicle and lower abdominal wall with eversion of the posterior bladder wall these changes are either partial or complete Adenocarcinomas develop from sequential changes initiated by chronic inflammation—from Brunn's epithelial cell mass, to cystitis cystica, to cystitis glandularis and finally to carcinoma which may or may not form mucin. Grossly fungating masses of tumor ulcerate the mucosa and invade the bladder wall. The surface in the mucoid type is covered with thick slimy gelatinous material. Adenocarcinoma also may arise from the urachus. The urachus measures 5 to 6 cm. in length and can be divided into the extravesical portion lying above the bladder and the intramural area within the wall The urachal lumen is continuous with the lumen of the bladder in about 33 per cent of the cases (Rappoport)

Most neoplasms arise from the intramural portion of the urachus and grow into the wall of the bladder There may be no evidence of mucosal ulceration

Microscopically adenocarcinomas are usually fairly well differentiated and produce much mucin. Rather frequently transitional cell carcinoma is associated



Fig 581 —X ray of the pelvis in a patient with exstrophy of the bladder with typical separation of the symphysis pubis (W U neg 49 2468)

Fig 582 —Clinical photograph of exstrophy of the bladder with carcinoma arising from it. (W U neg 48-1807)

Fig 583 —Photomicrograph of the tumor shown in Fig 582 It is the usual well differentiated adenocarcinoma. (×200) (W U neg 49-6721)

with them. This finding rules out a diagnosis of metastatic carcinoma (Saphir) In the bladder mucosa there are characteristic changes of cystitis cystica and cystitis glandularis in close proximity to the tumor The exact site of origin of

these tumors has not been established. Tubular structures are found in the fundus of the normal bladder near the medium umbilical ligament (urachus) (von Möllendorff Saphir) These tubular structures are embryonal remnants of the urachus and may be the site of adenocarcinoma (Wheeler) Squamous and transitional cell carcinomas of the exstrophied bladder can also occur

TRANSITIONAL AND SQUAMOUS CARCINOMA

Predisposing Factors

Aniline dye workers are known to develop carcinoma of the bladder rather more frequently than others (Bonser) These tumors can be produced experimentally by aniline dyes (Hueper) Barsotti found that benzidine and beta naphthylamine have the highest carcinogenic power Patch reviewed 12 cases of leukoplakia associated with carcinoma. There is little doubt that leukoplakia may follow prolonged chronic inflammation and undergo gradual transition to epidermoid carcinoma.

Carcinoma of the bladder *is a transitional cell tumor in a high percentage* of instances In spite of the regular and uniform microscopic pattern these tumors may locally recur and can easily be implanted in the abdominal wall Because of their prominent tendency to recur locally and because the microscopic pattern does not always conform with clinical behavior even the benign appearing papilloma should be classified as transitional cell carcinoma, Grade 1 This terminology has been adapted by the Bladder Tumor Registry and by the Armed Forces Institute of Pathology (Ash)

Lund followed 183 patients who had single or multiple papillomas (transitional cell carcinoma, Grade 1) 165 were followed for an average period of six months. "In the present series *34 per cent* of the solitary and *74 per cent* of the multiple papillomas recurred Of 137 solitary tumours *7 (5 per cent)* recurred as carcinomas of 44 primarily multiple papillomas *8 (18 per cent)* recurred as malignancies (Lund)

Grossly these tumors are a soft pink color and have a delicate frondlike papillary structure which cystoscopically looks like ferns suspended by pedicles (Fig 584) The more malignant lesions are frequently sessile and ulcerated. Transitional cell carcinomas of the bladder are usually located in the region of the trigone (75 per cent of instances) Therefore, partial to complete block of one or both ureters is frequent. The resulting hydronephrosis and pyelonephritis may produce serious renal damage and impair chance of successful bladder resection. A description of these tumors based on a series studied by Royce at Barnes Hospital is as follows

Grade 1—In 38 Grade 1 tumors 26 were pedunculated but there were 6 which were sessile. Only 6 of the group had necrosis. Microscopically regular frondlike papillary masses were separated by evenly spaced connective tissue septa. Individual cells were uniform and transitional in appearance with an abundant cytoplasm. Mitotic figures were few in number (Fig 585)

Grade 2.—Of 23 tumors 12 were pedunculated and 6 were sessile. Some degree of necrosis was present in 2 Microscopically the papillary nature of the

tumor persisted and the connective tissue septa were more irregularly spaced ol embracing relatively large masses of cells. In focal areas mitotic figures were quent and in some zones homogeneously staining nuclei had little accompany cytoplasm (Fig 586)



Fig 584—Gross photograph of cystectomy specimen with papillomatosis involving the e bladder with an area of invasive carcinoma (W U neg 50-4918)

Grade 3—A high percentage of these tumors were sessile and/or cauliflo like in appearance, necrosis and ulceration were common. Microscopic papillary areas were still present but these were irregularly distributed. The masses were in smaller groups and mitotic figures were often abundant (Fig 5

Grade 4—Most of these lesions were sessile, necrotic ulcerated and c flower like. Microscopically papillary areas were rare Small nests of tumor could be recognized only by their small homogeneous deeply blue staining nu The cytoplasm was small in amount mitotic figures were frequent and o atypical (Fig 588)

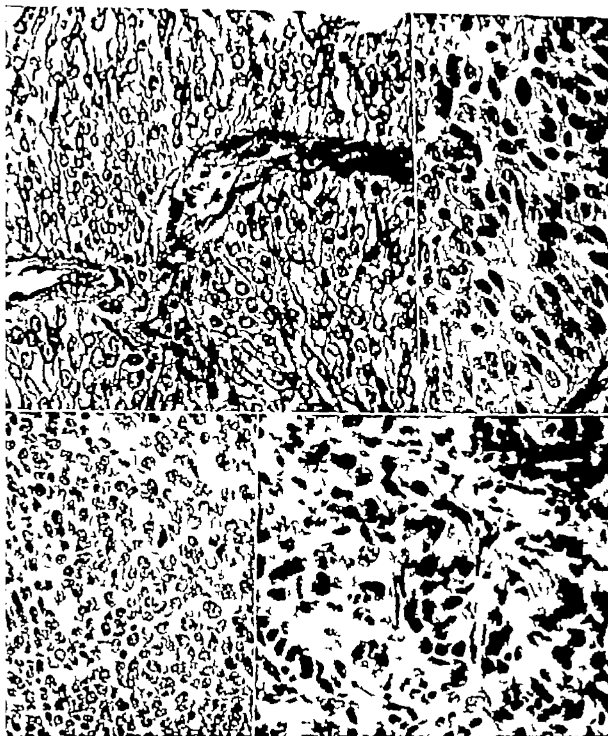


Fig 585 —Photomicrograph of grade 1 transitional cell carcinoma Note excellent differentiation of cells abundant cytoplasm, and few mitotic figures. (×400) (W U neg 49-545)

Fig 586 —Photomicrograph of grade 2 transitional cell carcinoma. Note variation in cell size, increase in prominence of cell nuclei and numerous mitotic figures. (×400) (W U neg 49-544)

Fig 587 —Photomicrograph of grade 3 transitional cell carcinoma Note loss of any pattern with considerable cell variation. (×400) (W U neg 49-547)

Fig 588 —Photomicrograph of grade 4 transitional cell carcinoma There is complete disorganization with extreme variation in size and shape of cells. (×400) (W U neg 49 549)

EPIDERMOID CARCINOMA

Of 135 consecutive cases of cancer of the bladder only 12 were squamous carcinoma (Royce) In practically all instances there were marked chronic inflammatory changes and associated leukoplakia (Figs 589 591) Grossly these tumors are usually ulcerated and necrotic. Microscopically they are undifferentiated squamous carcinomas, frequently showing small areas suggesting undifferentiated transitional cell carcinoma (Fig 592)

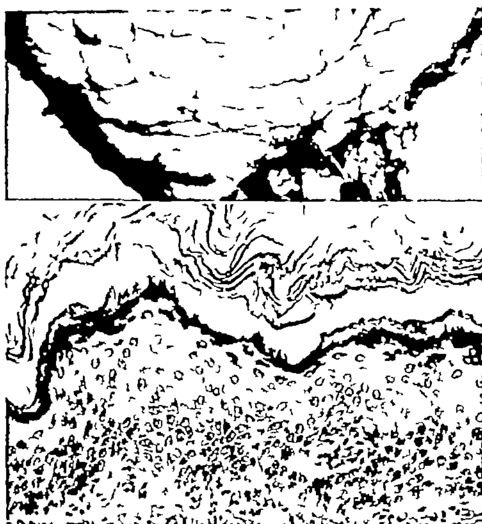


Fig 589 —Gross photograph of prominent leukoplakia of the bladder Note plaquelike areas of piled up epithelium. (W U neg 49-6452)

Fig 590 —Photomicrograph of extreme leukoplakia of the bladder The lining is made up of stratified squamous epithelium. (×220) (W U neg 49 2023)

GRADING OF CARCINOMA

The grading of carcinoma of the bladder is of prognostic significance only in large series of cases The frequency of variations in the grade prognosis correlation make grading of little value in the individual case The differentiation of a given neoplasm may vary from area to area and biopsies tend to show a lower degree of malignancy than is present in the surgical specimen. If the tumor is

very poorly differentiated at biopsy, this has prognostic significance (Jewett) If on the other hand, the lesion is well differentiated this does not mean that it might not be poorly differentiated in other areas (Melicow)



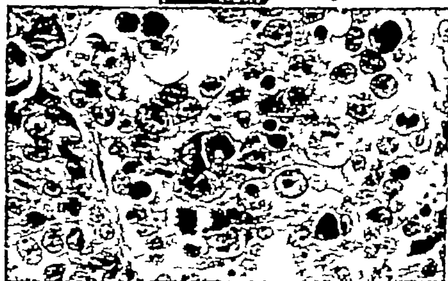


Fig 591 —Gross photograph of epidermoid carcinoma of the bladder with leukoplakia. (W U neg 50-4372.)

Fig 592—Photomicrograph of undifferentiated squamous carcinoma of the bladder (×400) (W U neg 49-552.)

CLINICOPATHOLOGIC CORRELATION AND PROGNOSIS

In our group of 135 patients, Grade 1 and Grade 2 carcinomas often presented with hematuria probably because of their great vascularity but did not as a rule have dysuria. Dysuria was usually associated with the Grade 3 and Grade 4 carcinomas very likely the result of infection and involvement of bladder wall. The more undifferentiated the tumor the worse the prognosis. In fact, any patient

with a Grade 3 or 4 carcinoma has an extremely poor prognosis and for this reason deserves radical therapy. The prognosis of the patients with tumors located on the dome and anterior surface of the bladder is much worse than of those with tumors located at the base of the bladder. Invasion of the wall of the bladder, possibly because of its rich network of lymphatics prejudices cure (Fig 593). In



Fig 593 —Photomicrograph to demonstrate extensive growth of bladder carcinoma within the lymphatics of the bladder musculature (×97) (W U neg 49 550)

Non-infiltrating
Infiltrating
Superficial
Deep
Group A
Group B1
Group B2
Group C
Mucosa
Submucosa
Muscle
Perivesical Tissue and Lymphatics

Fig. 594 Schematic representation of depth of invasion of bladder cancer The more superficial the tumor the better the prognosis. (From Jewett, H J J Urol 67 672 1952.)

segmental resection and cystectomy specimens Jewett demonstrated excellent correlation between the depth of invasion and the prognosis (Fig 594) The prognosis of any group of patients with carcinoma of the bladder reported in the literature is influenced to a considerable extent by the number with Grade 1 carcinomas Study of cystectomy specimens may show zones of focal atypical proliferation or early carcinoma in areas remote from the main tumor mass (Fig 595) Such lesions indicate that carcinoma of the urinary bladder may have multiple foci of origin These findings reinforce the argument for cystectomy At present operative mortality is low and pyelonephritis is no longer a common complication if

conduit ureteral diversion is accomplished by implantation of the ureters into an isolated segment of ileum. In 48 cystectomies for carcinoma of the bladder there were only 2 operative deaths and 16 five year survivals (Cordonnier)



Fig 595 —Photomicrograph of apparently normal bladder epithelium taken at a distance from an invasive carcinoma. These changes represent early carcinoma and suggest multiple foci of origin. (×250) (W U neg 52-604)

RARE TUMORS AND LESIONS

An apparently benign mucin secreting *cystadenoma* was reported by Govan. *Carcinoma of the signet ring type* has been reported by Saphir Pollack reported a *malignant teratoma* of the urinary bladder Rathbun (1944) reported a case of *lymphosarcoma* in which there were two smooth irregular ulcerated tumors on the lateral wall of the bladder Jacobs believes that patients with lymphosarcoma have a fairly good prognosis. The bladder can be involved by *leukemia* (Pentecost)

Polypoid rhabdomyosarcoma (sarcoma botryoides) is a rare tumor which usually appears in children. It has a mucoid polypoid appearance stubbornly recurs, infiltrates surrounding tissues, and kills by direct extension rather than by distant metastases (Mostofi) (Fig 596) Microscopically it shows myxomatous tissue in which striated tumor cells often can be seen. The only hope of cure is radical surgical resection (Fig 597)

Fig 596 —Gross photograph of sarcoides botryoides of the bladder with characteristic polypoid masses This 40-year-old woman is living and well two years later (W U neg 56-4?09)

Fig 597 – Photomicrograph of a polypoid mass of tumor in sarcoma botryoides. This lesion occurred in the bladder of a 4 year-old boy (Low power) (W U neg 58-1449)

Malakoplakia of the bladder is an extremely rare lesion in which there are multiple nodular thickenings of the mucosa and submucosa, usually in the region of the trigone, which may be mistaken for cancer (Bleisch) Microscopically there are multiple rounded cells with granular acidophilic cytoplasm beneath the lining cells. Within some of these cells are rounded concentrically layered intra cytoplasmic inclusions which may give a positive reaction for inorganic iron. This is a nonneoplastic lesion of unknown etiology (Putschar)

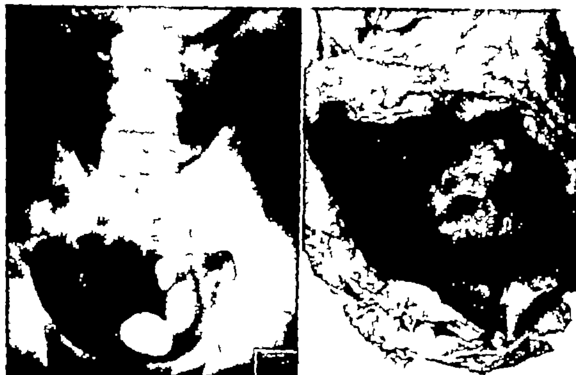


Fig 598.—Radiograph and gross specimen demonstrating several bladder calculi (W U negs. 49 7082 and 40-7083)

Bladder calculi occur more commonly in males than females in Wishard's series there were 225 males and 17 females. In this country stones occur most commonly in elderly patients. Usually the stone is single. The most common associated abnormality is hypertrophy of the prostate. The stones are often phosphates urate and oxalate stones are less common (Twinem) Treatment is removal either via urethra after crushing the stone or by cystostomy Recurrence appears in about 10 per cent of the cases.

Regeneration of the bladder following gangrenous cystitis was reported by Garrett.

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Chapter 16

MALE REPRODUCTIVE SYSTEM

PROSTATE AND SEMINAL VESICLES

INTRODUCTION

Pathologic study of the prostate is generally made on tissue obtained by punch biopsy transurethral resection, suprapubic prostatectomy and infrequently by radical perineal prostatectomy When the entire prostate is submitted, large sections should be made of the posterior lobe and of the prostate and adjoining seminal vesicle.

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MALE REPRODUCTIVE SYSTEM

PROSTATE AND SEMINAL VESICLES
TESTIS
EPIDIDYMIS AND SPERMATIC CORD
PENIS

PROSTATE AND SEMINAL VESICLES

INTRODUCTION
ASPIRATION AND PUNCH BIOPSY
CYTOLOGIC EXAMINATION OF SECRETIONS FROM THE PROSTATE
FROZEN SECTION
HYPERTROPHY
INFARCTION
CALCULI
GRANULOMATOUS PROSTATITIS
TUBERCULOSIS
RARE INFECTIONS
CARCINOMA
  Microscopic Changes Produced by Orchiectomy and Estrogen Therapy
RARE TUMORS
SEMINAL VESICLES

INTRODUCTION

Pathologic study of the prostate is generally made on tissue obtained by punch biopsy, transurethral resection, suprapubic prostatectomy, and infrequently by radical perineal prostatectomy. When the entire prostate is submitted, large sections should be made of the posterior lobe and of the prostate and adjoining seminal vesicle.

In early carcinoma transurethral resection does not reveal cancer. It is almost impossible to section all the material usually submitted. McHeffey examined

ten pieces of tissue from each of 50 cases and then took time to examine all the remaining pieces in the same 50 cases one additional carcinoma was found

ASPIRATION AND PUNCH BIOPSY

There are many special types of needles and punches which have been devised for obtaining prostatic tissue (Peirson) Carcinoma of the prostate usually arises in the posterior lobe, so that before a positive diagnosis can be made by transurethral biopsy the disease is advanced In most instances a positive diagnosis can be obtained only by aspiration or Silverman needle biopsy if performed by a surgeon experienced in this method (Fig 599) The risk of implantation following needle biopsy is extremely low only a single instance has been reported (Clarke)

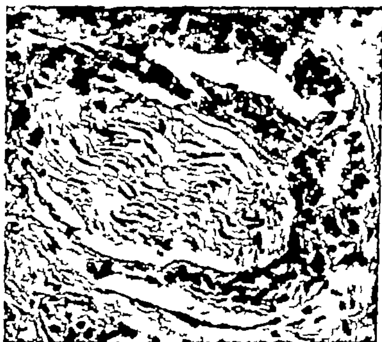


Fig 599 —The patient had a well-delimited small nodule in the prostate Transurethral resection did not show carcinoma Punch biopsy demonstrated well-differentiated carcinoma and nerve sheath invasion in one area (×400) (W U neg 52 2874)

An increasing number of transrectal needle biopsies of the prostate have been done for debatable nodules. This procedure has proved to be accurate in needling the nodule and has also been rewarding because of the adequate material that has been obtained (Pearlman) The material obtained should be blocked and prepared the same as other tissue sections. Ferguson reported that from 50 aspirations of the prostate good material was obtained in 39 A diagnosis of carcinoma was made in 28 patients 27 had died of cancer at the time of the report.

CYTOLOGIC EXAMINATION OF SECRETIONS FROM THE PROSTATE

Herbut examined the secretions from 100 patients and made a positive diagnosis of carcinoma in 17 diagnosis was confirmed histologically in 16 of these patients. He made the diagnosis of carcinoma of the prostate on the basis of increase

in the size of cells replacement of clear cut cell membrane by a fuzzy border, a relative or absolute decrease in the amount of cytoplasm and increase in the size of the nucleus At times there were prominent nucleoli These changes seem minimal and in our experience do not yield information of practical value Furthermore it does not seem wise to massage a carcinoma of the prostate Cells exfoliated from the normal seminal vesicles may be extremely bizarre

FROZEN SECTION

A firm area in the region of the posterior lobe of the prostate close to the capsule may or may not be malignant frozen section is usually done solely to rule out carcinoma The type of surgical exposure advocated by Hudson facilitates frozen section he obtains a representative section of the entire posterior lobe If the lesion is obviously cancer and particularly if there is evidence of nerve sheath invasion there should be no hesitation about the treatment In some instances a benign process such as tuberculosis infarct or a calculus may be obvious. Often however adenocarcinoma of the prostate is well differentiated, and a frozen section diagnosis may not be possible Totten has emphasized that normal prostatic glands have a double layer of cells with flattened basal cells against the basement mem brane In cancerous glands there is a single layer of cells with prominent nucleoli These findings are particularly helpful in well-differentiated carcinomas where the diagnosis must be based on the crowding of glands and cytologic abnormalities. Nerve sheath invasion is definite evidence of carcinoma. The accuracy of frozen section is high in 45 cases reported by Culp there were no false positives and all 40 cases of cancer were substantiated Clinical appraisal of single nodules is ex tremely difficult In 46 perineal prostatectomies performed on clinical diagnoses of carcinoma there was no carcinoma found in 19 instances (Colby)

HYPERTROPHY

Benign prostatic hypertrophy is the most common name applied to the benign condition of the prostate which occurs in elderly men Moore's term nodular hyperplasia" is a more exact designation Prostatic hypertrophy increases in in cidence with age until at 80 about 75 per cent of all men have evidence of this entity

The gross specimens usually come from a suprapubic prostatectomy rarely from perineal prostatectomies The glands are enlarged averaging around 100 grams but extremely large glands (weighing up to 820 grams) have been reported (Ockerblad) On cross section multiple spherical adenomatous yellowish nodules project above the cut surface (Fig 600) The stroma consists of connective tissue and smooth muscle The early nodule is slightly elevated and gray or grayish yellow with a finely or coarsely granular cut surface *Suprapubic prostatectomy* is the enucleation of only newly formed nodules the prostate itself is not resected. After suprapubic prostatectomy the compressed posterior and lateral lobes expand by stromal growth to surround the prostatic urethra. Because this operation is not a complete prostatectomy nodular hyperplasia can recur Over 30 cases of recur rence have been reported (Moore)





Fig. 600 — Gross photograph of material obtained from a suprapubic prostatectomy Note nodulation of surface Weight, 360 grams. (W U neg 50-1685)

Fig. 601 — Photomicrograph of early hyperplasia of the prostate beginning in the suburethral tissues (Low power) (W U neg 49-5634)

Microscopic description According to Moore,

> The earliest lesion that has been observed is a proliferation of the peri vascular periductal or intralobular connective tissue in an area bounded medially by the urethra anteriorly by the capsule and posteriorly and laterally by the sweeping ducts of the lateral lobes and in the tissues that constitute the middle lobe (Fig 601) The type of connective tissue involved depends in large part on the area Near the urethra the proliferation is about small sinusoidal spaces while in the glandular parts the periductal or intralobular stroma is hyperplastic

With increased growth the lateral lobes are pushed aside and compressed Nodules of prostatic hypertrophy are most commonly derived from the stroma and glands about the urethra and the acini anterior and medial to the ducts of the lateral lobes The true middle lobe of the prostate is less frequently involved, the anterior lobe rarely and the posterior very rarely if at all The well-developed nodules are divided into lobules by an inter and intralobular stroma. The typical epithelial cell in prostatic hypertrophy resembles that of the adult prostate but differs in relative absence of secretory activity These glands are lined by tall epithelium sometimes with papillary infoldings, and have a well-developed basement membrane The stroma differs from normal there is more smooth muscle and absence of elastic tissue Periurethral tissues have abundant elastic tissue. In periductal hyperplasia the proliferation may be concentric or eccentric in intralobular hyperplasia there may be a pure stromal reaction or a combined stromal and epithelial hyperplasia However prostatic hypertrophy usually is associated with the development of masses of glandular tissue Nodules composed only of smooth muscle arising in periurethral tissue represent a variant in which the stromal hyperplasia does not include glands.

From histologic studies it is evident that the important point is not whether the periurethral or prostatic glands are involved but whether the lesion occurs in a glandular acinus the duct of which empties into the urethra above or below the caudal extremity of the verumontanum The earliest nodules may be demonstrated in acini of the middle and lateral lobes of the prostate and about the collicular and subtrigonal periurethral glands all structures which empty cephalad to the verumontanum. In only 1 out of 700 prostates has a nodule been demonstrated in the posterior lobe, which empties caudal to this point (Moore) The only possible conclusion from these morphologic observations is that the stroma of the prostate cephalad to the verumontanum reacts to different stimuli or to a greater extent to the same stimuli than stroma caudal to the verumontanum. The posterior lobe of the prostate may be biologically different from the other lobes. This latter view is strengthened by the observation that in the senile prostate atrophy occurs at an earlier age corpora amylacea are more abundant, and sclerotic atrophy and stromal fibrosis are more marked in the posterior lobe than in the other lobes.

Hypertrophy causes urinary obstruction which requires surgical intervention Moore feels that the urinary obstruction may be a physiologic mechanism based on dysfunction of the internal sphincter He questions whether the results of prostatectomy are not the result of the destruction of the internal sphincter

INFARCTION

Infarction of the prostate has been well described by Abeshouse. It occurs predominantly in adenomatous large prostates its incidence is probably related to the thoroughness of the microscopic examination In very carefully studied glands Moore demonstrated *infarction in 25 per cent. Baird found 66 instances in 352*





Fig 602 —Gross photograph of infarct of the prostate showing sharp delimitation and areas of hemorrhage Nodular hyperplasia and hypertrophy are also present. (W U neg. 48-3984)

Fig 603 —Photomicrograph of margin of infarct shown in Fig. 602 demonstrating prominent squamous metaplasia often mistaken for carcinoma (×100) (W U neg 48-4162)

surgically enucleated prostates However the frequency of clinical manifestations of infarction is much lower

The mechanism of infarction is unknown but may be related to the presence of infection trauma due to indwelling catheter cystitis or prostatitis The ureteral arteries penetrate to the prostatic vesicle junction and then turn distally in a course parallel to the urethral surface bringing blood to the area of usual adenomatous growth Damage or thrombosis of these arteries causes infarction to a major portion of an adenomatous gland (Flocks) Baird has shown that the size and number of infarctions are related directly to the degree of prostatic hyperplasia

Grossly these lesions vary in size from a few millimeters to 4 or 5 cm They are speckled grayish yellow and often contain streaks of hemorrhage The peripheral margins are usually sharp and hemorrhagic (Fig 602) Such areas of infarction impinge upon the urethra and occur only in zones of hyperplasia (Baird) Microscopically an ischemic infarction shows areas of central coagulation and necrosis with complete destruction of the muscle epithelium and connective tissue The most striking changes are in the periphery Extremely prominent epithelial metaplasia may occur True squamous metaplasia is infrequent and intercellular bridges and keratinization are rare (Fig 603) Mitotic figures are rare and direct invasion of surrounding prostatic tissue is absent It is unlikely that metaplasia will be mistaken for squamous carcinoma if the pathologist remembers that metaplasia is normally associated with infection and is confined to the ducts *Epidermoid carcinoma of the prostate is a pathologic rarity* Clinically infarction occasionally causes acute urinary retention through rapid prostatic enlargement (Hubly) Because the infarcts are adjacent to the urethra there may be gross hematuria Diffuse oozing of blood from the overlying mucosa may be seen cystoscopically (Roth)

CALCULI

Prostatic calculi usually are associated with infection They may occur concomitantly with carcinoma or nodular hypertrophy and hyperplasia the frequency with which they appear with either is approximately 7 per cent (Cristol)

Young studied 100 cases of prostatic calculi and found stones located in the utricle in one case and within the prostatic fossa following prostatectomy in five cases. Calculi found in the prostatic urethra may have their origin from the bladder ureter or kidney pelvis and are not true prostatic calculi (Lowsley) In Young's group of 44 operative specimens infection was invariably present either in the prostatic duct or acini about the calcification Calculi may form in the ducts or acini which are blocked by bacterial or epithelial debris the corpora amylacea may act as a nucleus for stone formation Certainly improper drainage of the prostate due to stricture of the vesicle neck may lead to infection and the formation of calculi When acini become infected and dilated small bits of calcium are deposited upon the corpora amylacea and other foreign substance (Lowsley) Calculi usually are present in the line of cleavage between nodular hyperplasia and the posterior prostatic lamella The nucleus of a prostatic calculus is composed of corpora amylacea blood clot epithelial detritus, bacteria or tissue.

The inorganic element usually is inorganic salt—calcium phosphate, magnesium phosphate ammomagnesium phosphate, potassium phosphate calcium carbonate, and calcium oxalate.

The diagnosis of calculi is more frequently made by x ray than by rectal examination because the stones are radiopaque (Fig 604) *Because of their hardness* they may be erroneously diagnosed as carcinoma If the process becomes advanced prostatectomy is indicated (Henline) (Fig 605)

GRANULOMATOUS PROSTATITIS

Granulomatous prostatitis is relatively rare (Tanner) its pathogenesis is *probably related to partial obstruction of the prostatic ducts and urethritis. These* changes are accompanied by destruction of the epithelial cells of the ducts and acini plus escape of inflammatory products and altered prostatic secretion into the interstitial tissue.

Grossly the consistency of the prostate may be firm or stony hard Invariably *nodular hyperplasia and hypertrophy are present. On section the architecture* of the gland may be obliterated Microscopically granulomatous prostatitis is usually confused with neoplasm less often with tuberculosis. In some areas the normal acini and ducts are completely destroyed and replaced by an exudate of plasma cells lymphocytes, and in part by large pale staining mononuclear cells *with slight eosinophilic cytoplasm (Fig 606) Tubercle like reaction with foreign* body giant cells is seen At times there are collections of polymorphonuclear leukocytes and detritus within the ducts. There are no crystals nor in our cases have tubercle bacilli been identified this lesion is not syphilitic.

Clinically this lesion usually occurs in patients over the age of 50 In 9 of 32 cases reported by Tanner the preoperative diagnosis was probable carcinoma. The firmness of the lesion is caused by replacement of areas of the prostate by dense fibrous tissue.

TUBERCULOSIS

Tuberculosis of the prostate usually follows hematogenous spread from the lungs or less often from foci in bones. Autopsy studies show the prostate frequently involved by the infection when tuberculosis of the male genitalia exists. Of 105 cases studied by Auerbach 100 had prostatic involvement and in 35 it was the only tuberculous organ Rarely tuberculosis directly invades the prostate from the urethra *2 of 20 cases of tuberculosis of the prostate described by Moore were in*fected in this manner

Grossly the lesions most frequently appear in the lateral lobes and are much more often bilateral than unilateral The initial lesion arises in the interstitial tissue but quickly spreads to the acini and forms a caseous mass with a connective tissue wall Confluent caseous zones occur with liquefaction and cavitation until finally the prostate becomes an enlarged mass of multiple cavities (Fig 607) If this tuberculous process becomes secondarily infected, it often perforates into the urethra and involves the urinary bladder 14 of Auerbach's 105 cases showed secondary involvement of the bladder With still further spread sinus tracts may





Fig 604 —Radiograph of radiopaque calculi in the prostate Such lesions on palpation are often mistaken for carcinoma

Fig 605 Gross photograph of large prostate with a radiopaque calculus (W U neg 48-5595)

Fig 606 – Photomicrograph of granulomatous prostatitis often mistaken for carcinoma both on palpation and microscopic examination. Note inflammatory process around the duct. (130) (W U neg 58-1450)



Fig 609 —Gross photograph of early carcinoma of the prostate arising in the posterior lobe (Courtesy Dr Robert A. Moore Washington University School of Medicine St. Louis, Mo.)

Fig 610 —Gross photograph of a large ... ounding ... mited honey-combed ... lar hy ... neg 5

An acinar basement membrane may be absent in an undifferentiated carcinoma (Moore) but present in well-differentiated carcinomas. Epithelium formed in early carcinoma often shows small acini, numerous papillae, increased columnar and cuboidal cells, and a relatively dense deeply acidophilic cytoplasm. Carcinomas may be extremely undifferentiated, very soft, and contain large amounts of fat. The presence of nerve sheath invasion by a well-differentiated tumor is absolute proof of carcinoma.

It is sometimes very difficult to determine the primary source of advanced cancer in the region of the prostate, the same problem may arise when prostatic carcinomas invade the region of the rectum. The prostatic origin of such tumors is definite if tissue from a metastasis or from a locally invasive mass has an acid phosphatase activity exceeding 10 units (Dean). Positive mucin stains rule out prostatic carcinoma in most instances.

Microscopic Changes Produced by Orchiectomy and Estrogen Therapy

Carcinoma of the prostate may locally regress and become soft following estrogen therapy and orchiectomy. Histologically the tumor cells become pyknotic, show increased staining density, and frequently have naked nuclei (Figs. 611 and 612). Vacuolization of the cytoplasm occurs, the cytoplasmic membrane may rupture and in some instances only shadows of cells remain. With estrogen therapy squamous metaplasia may occur in the nonneoplastic glands (Bainborough) (Fig. 613). Wattenberg also found increased stratification with true squamous metaplasia in the urethra and verumontanum (Fig. 614). These changes are specific estrogenic effects. Intraductal hyperplasia and stromal proliferation in the breast may cause the patient to complain of sore breasts and discharge from the nipples. Rarely true acinar proliferation and lobule formation may occur.

Suprapubic prostatectomy and simple perineal prostatectomy do not remove completely the compressed lateral and posterior lobes. In these lobes carcinoma may develop many years after operation.

When prostatic carcinoma extends to the bones, surrounding soft tissue, or lymph nodes, the serum acid phosphatase may become elevated. This elevation is evidence of advanced disease, the only exception being transient elevation in the presence of prostatic infarct. Removal of an area of infarction promptly returns the acid phosphatase to normal (Stewart). Deming demonstrated by heterologous growth of prostatic cancer that the acid enzyme factor was low in some clinical cases with extensive metastatic carcinoma; large amounts of acid phosphatase were not always produced.

The clinical detection of carcinoma of the prostate by rectal examination often is difficult because early carcinomas cannot be distinguished from benign prostatic nodules. Some authors advocate more frequent perineal exploration of debatable nodules with frozen section examination, followed by radical perineal prostatectomy if cancer is found. Usually this method is stated to be the only certain method of curing early carcinoma of the prostate. The number of such operations in any given hospital is small. Jewett reported radical perineal prostatectomy in 320 patients; if the cancer was confined to the prostate, the ten year survival was 49 per cent. Against radical operation for carcinoma of the prostate is the morbidity

ination distant metastases and local invasion beyond the prostate are unusual. We have found that the pathologist can help the clinician in deciding whether there should be further therapy for patients in whom cancer is found unexpectedly in suprapubic enucleations Patients with small well-differentiated cancer regardless of the use of antiandrogenic therapy have a ten year survival rate that is almost the same as noncancerous males of the same age group For such cases we favor no further therapy However, patients with large or less than well-differentiated cancers do poorly (ten year survival rate 14 per cent) and for these we are in favor of secondary radical surgery The published work on unsuspected carcinoma found in the transurethral resections offers no clear evidence either for or against further surgical therapy (Bauer) We are not in favor of perineal prostatectomy for patients with nodular hyperplasia and hypertrophy



Fig. 615—Clinical photograph of adenocarcinoma of Cowper's gland invading the scrotum and perineal region. (EFSCH 46-8564)

RARE TUMORS

Sarcoma of the prostate often occurs at an early age. Many of these tumors are so extremely undifferentiated that it is impossible to classify them. Well-defined examples of *rhabdomyosarcoma leiomyosarcoma* and *fibrosarcoma* have been reported (Stirling Khoury Rappoport) Stirling believes that sarcomas of muscle origin are the most common. Many round-cell sarcomas are probably undifferentiated carcinomas. Sarcomatous prostates are usually large firm smooth and difficult to differentiate from nodular hyperplasia and hypertrophy Urinary infection or obstruction is common We have seen an *adenocarcinoma of Cowper's*

gland which ulcerated the skin of the scrotum (Fig 615) and *primary lymphosarcoma* of the prostate (King) *Epidermoid carcinoma* has been reported by Sieracki

SEMINAL VESICLES

Tuberculosis of the seminal vesicles is invariably secondary to infection in the prostate the greatest amount of involvement is found adjacent to the prostate Auerbach has seen five cases in which only the seminal vesicles were involved These were probably hematogenous in origin *Cysts* arising from the ducts of the seminal vesicle are rare (Lund)

Primary malignant tumors of the seminal vesicle are pathologic curiosities Many of the reported cases probably represent invasion from carcinoma originating in other sites particularly the prostate In order to make a diagnosis of primary carcinoma of the seminal vesicle there must be no involvement of the prostate, and the microscopic pattern must be compatible with seminal vesicle origin In an overall critical review of the literature Lazarus felt that there were only seventeen authentic instances of primary cancer of the seminal vesicle

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TESTIS

CRYPTORCHIDISM

At times the testis does not descend normally and is retained within the abdomen or inguinal region The inguinal testis is about four times as common as the abdominal one. However in the retained abdominal testis tumors occur more frequently suggesting that hormonal factors may play some role (Campbell) These testes are small and brown Microscopically the tubules are atrophic, and interstitial cells are prominent (Figs. 616 and 617) Malignant tumors occurring in retained testes are usually seminomas. If by the age of 6 years the abdominally retained testis has not spontaneously descended to the scrotum the administration of gonadotropin may cause its descent. If this therapy is unsuccessful, the testis should be placed in the scrotum by operation. This must be done by the time the child is 6 otherwise permanent anatomic alterations will occur (Robinson) The testicular tubules will become atrophic and, therefore, the increased risk of a malignant tumor (particularly seminoma) will be just as great as if the testis had remained within the abdomen (Hinman) Sohval reported the interesting observation that in 29 adult patients with malignant testicular tumor occurring in a normally placed testis foci of seminiferous tubules of the prepubertal type were found. This observation suggests that testicular tumors do not occur in a normal testis "The incidence of cryptorchidism is 0 23 per cent. The incidence of cancer in the cryptorchid testis is *11 per cent*. The incidence of cancer in the normally located testis is only 0 0015 per cent The incidence of cryptorchidism in over 7 000 patients with testis cancer is 10.9 per cent." A high inguinal or abdominal cryptorchid testis does not descend. If it is placed in the scrotum the testis still may develop cancer Apparently such a testis *does not become normal when placed in the scrotum*. There are over 80 reported cases of malignant neoplasms occurring in testes that have



Fig 616 Extreme atrophy in a cryptorchid testis in a 42 year-old man There is tremendous thickening of the wall of the tubules and only scattered Sertoli cells are seen. (×350) (W U neg 58-1453)

Fig 617—Photomicrograph of a cryptorchid testis in a 12 year-old boy The tubules are of the prepubertal type Note contrast to Fig 616 (×250) (W U neg 58-1452.)

been surgically placed in the scrotum It is because of the statistics quoted and the reasons stated that some urologists believe that all unilateral high inguinal or abdominal cryptorchid testes should be excised (Baker) Gross believes that the risk of cancer in abnormally placed testes is exaggerated and he maintains a rather conservative attitude to their removal. He has shown that in bilateral cryptorchidism, if the testes are placed in the scrotum in the prepubertal period, about 80 per cent will have acceptable fertility He emphasizes the great importance of care in doing the operation in order that the fragile blood supply to the testes not be damaged.

The basis of the decision to place a cryptorchid testis in its normal position if it fails to descend before the age of 6 is based on a careful study of the normal developing testis and its comparison with the cryptorchid testis. Charny has summarized the normal testicular development as follows

> The child testis begins as an organ composed of small seminiferous tubules compactly filled with small undifferentiated cuboidal cells. Increase in tubule and cell size is slow and gradual. Tortuosity and lumen formation first appear at age 4 and, with this a most orderly arrangement of the cells which become identifiable as spermatogonia. Leydig cells cannot be seen except in the newborn. This slow barely perceptible growth continues up to age 10 at which time a definite spurt is noted. Mitotic figures now appear in the cells of the tubule and Leydig cells are seen in the intertubular spaces. At age 11 mitotic activity is pronounced Primary and secondary spermatocytes appear At age 12 spermatids are numerous. Finally spermatozoa appear Because of the great variation in the age at which puberty normally occurs, the age of the individual cannot be determined by histologic study of the testis after the twelfth year The number of maturing tubules with active spermatogenesis increases until the picture seen in the adult is reached. The age of the subject at the final stage of development varies from 11 to 15 years in our series
>
> It can be seen that although appreciable histologic changes are noted at almost yearly intervals it is possible to divide testicular growth and development into three major phases as follows
>
> 1 Static phase from birth to age 4
> 2 Growth phase from age 4 to age 10
> 3 Developmental (maturation) phase from age 10 to puberty
>
> It is interesting to note that the first appearance of tubular development as differentiated from tubular growth, occurs at age 10 and that this coincides with the age at which gonadotropins and 17 ketosteroids are first found in the urine in any appreciable quantity Testis maturation may therefore be said to begin at about age 10 and to progress over a period of 2 to 5 years until it is complete

PREPUBERTAL TESTES, ATROPHY AND INFERTILITY

Atrophy of the testis may follow mumps, orchitis or rarely some other inflammatory process. Testicular tissue also can be destroyed by local or total body irradiation or P^{32} (Platt) Atrophy may be associated with cirrhosis of the liver Atrophy of tubules and perhaps some interstitial cell hyperplasia are thought to be caused by circulating endogenous estrogens not detoxified by the diseased liver

(Bennett) The same pathologic changes can occur in the testes of patients who are being given estrogen for carcinoma of the prostate. In human beings prolonged stilbestrol therapy may cause pronounced atrophy with interstitial cell hyperplasia but as far as is known does not cause interstitial cell tumors as it may in animals After estrogen therapy, there is severe atrophy of the germinal epithelium Sertoli cells may completely disappear and there may be peritubular sclerosis Leydig cells may simulate fibroblasts or show adenomatous clusters (de la Balze)

Incisional biopsy of the testis is worth while in evaluating eunuchoidism and infertility Punch biopsies are not nearly so satisfactory Nelson described three patterns of eunuchoidism hypogonadotrophic eunuchoidism, 62 per cent, puberal seminiferous tubule and Leydig cell failure 25 per cent, prepuberal testicular failure, 13 per cent. Clinically the patients all have failure of normal puberal maturation undeveloped genitalia scanty extremity and facial hair, and eunuchoidal body proportions. In hypogonadotrophic eunuchoidism the tubules are small Sertoli cells undifferentiated the number of spermatogonia are decreased and the spermatocytes are few in number or absent. The intertubular areas lack characteristic Leydig cells but contain numerous precursors of these cells. The primary defect is in the hypophysis not the testis. In puberal seminiferous tubule and Leydig cell failure biopsy shows completely hyalinized tubules and atrophic, nonfunctioning Leydig cells. The Sertoli cells have oval nuclei and prominent nucleoli (Engle) This condition appears due to testicular failure at the onset of puberty In prepuberal testicular failure biopsy demonstrates either lack of testicular tissue or only atrophied testis This condition is the result of congenital aplasia of the testis or early atrophy due to trauma infection, or constitutional defectiveness. In infertility there may be complete azoospermia or oligospermia. With azoospermia the testicular biopsy may show normal tissue, in which case there is either bilateral obstruction or congenital absence of some portion of the excurrent ducts. However there may be complete fibrosis with extensive peritubular fibrosis and prominence of Leydig cells. Apparent thickening of the basement membrane of the tubules often is caused by an increase of collagen in the inner layers of the fibrous tunic directly beneath the basement membrane (Sniffen) If there is complete germinal cell aplasia the tubules usually are not significantly fibrotic but are populated almost exclusively by sustentacular cells. Germinal cell arrests occur in which spermatogenesis usually does not proceed beyond the primary spermatocyte Oligospermia may be due to variations of the above picture (Fig 618)

BENIGN TUMORS

Benign tumors of the testis are extremely rare. We have seen a few so-called tubular adenomas and interstitial cell neoplasms The borderline between hyperplasia, adenoma, and malignant tumors of interstitial cell type is hard to define

Interstitial cell tumors produce hormonal changes because of increased androgen production by the neoplasm. Precocious pseudopuberty occurs with growth of pubic hair and enlargement of the penis. The term pseudopuberty is used because spermatic function of the testis remains dormant (Jungck) These tumors

Fig 618.—Photomicrograph of testis in sterile male. There has apparently been germinal cell arrest as well as oligospermia. (×350.) (W U neg 58-1454.)

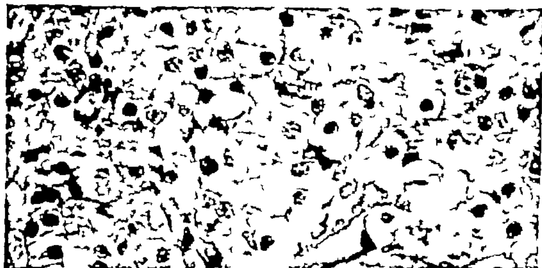


Fig 619.—Photomicrograph of an interstitial cell tumor of the testis in a child with precocious puberty. Removal of the tumor caused regression of symptoms. Individual cells are uniform with well-defined cytoplasmic outlines and no mitotic figures. (×540.) (W U neg 52-4341.) (Slide contributed by K. B. Fraser, Brisbane, Australia.)

are rare only about 40 have been reported (Nation Warren) Of 922 testicular tumors collected by Friedman only 9 were interstitial cell tumors. Rarely these tumors are bilateral (Flynn) they are rarely malignant (Nation) Grossly they are usually small reddish brown in color and are sharply delimited by the testis Microscopic examination shows tumor cells with well-defined cytoplasmic outlines and uniform nuclei (Fig 619) Lipochrome pigment may be present in the cytoplasm If Reincke's crystals (rod shaped crystalloids) are present they are best demonstrated by Masson trichrome stain (Sternberg) In the presence of the tumor the rest of the testis does not show interstitial cell hyperplasia Removal of the tumor causes regression of the precocious pseudopuberty (Fraser) Teilum and Lewis reported feminizing tumors of the testis arising from Sertoli cells Estrogen secreting Sertoli cell tumors are rather common in dogs (Scully)

MALIGNANT TUMORS

The classification of testicular tumors has shown numerous changes with the passage of time, but the classification used by Friedman is widely accepted and is used here It is well for the student in pathology to know the synonyms and various classifications the type of tumor influences treatment and prognosis.

CLASSIFICATION OF TESTICULAR TUMORS

1 Adult teratoma
2 Teratocarcinoma
3 Embryonal carcinoma
4 Choriocarcinoma
5 Seminoma

Testicular tumors make up only a small percentage of all malignant neoplasms but are the commonest malignant tumor in young men between 25 and 29 years of age. The Armed Forces Institute of Pathology collected almost 1 000 neoplasms of the testis during the war years. Testicular tumors are infrequent in children. Mostofi could collect only 24 cases 7 were teratomas with mature brain bone, cartilage, and skin 15 were embryonal carcinomas in 2 the diagnosis was uncertain Seminoma apparently does not occur in children.

Adult Teratoma

The adult teratomas make up 5 to 10 per cent of the neoplasms of the testis. They may become relatively large are cystic, and usually contain variable amounts of myxoid tissue and cartilage (Fig 620) Bone is infrequent. The dermoid type of teratomas which are so common in the mediastinum and ovary are rare in the testes. These cystic teratomas contain all types of tissue nerve, cartilage various types of epithelium, and connective tissue (Fig 621) Adult teratomas are rarely benign if sufficient sections are studied zones of malignant change are frequently found.

Teratocarcinoma (Malignant Teratoma)

Teratocarcinoma has a growth pattern similar to the adult teratoma except for soft areas of necrosis suggesting cellularity (Fig 622) Microscopically there may be various types of well-differentiated tissue but in addition there are



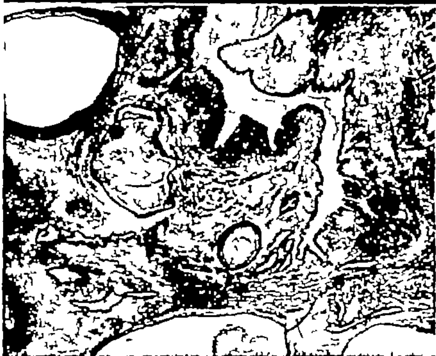


Fig 620 —Gross photograph of a large cystic teratoma. (AFIP 539341)

Fig 621 —Well-differentiated teratoma with cystic spaces and cartilage formation. (Low power) (W U neg 49-1519)



Fig. 622.—Gross photograph of a large teratocarcinoma containing various tissues. In many areas the tumor was undifferentiated. (W U neg 49-282)

Fig 623 —Photomicrograph of an area of adenocarcinoma in a teratocarcinoma. (Moderate enlargement.) (W U neg 47 744)





Fig 620 —Gross photograph of a large cystic teratoma. (AFIP 539341)

Fig 621 —Well-differentiated teratoma with cystic spaces and cartilage formation. (Low power) (W U neg 49-1519)

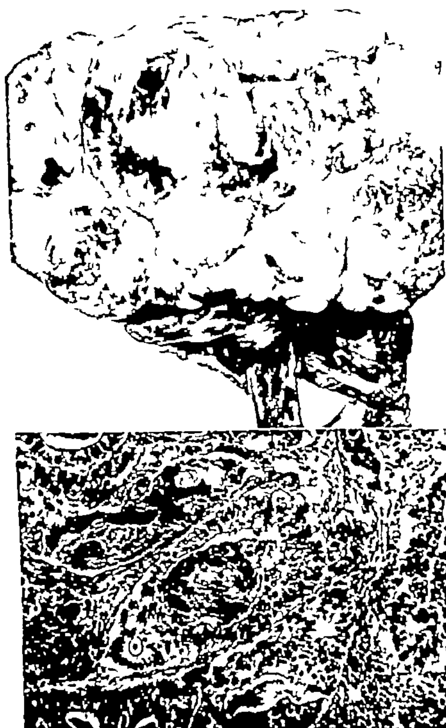


Fig 622 —Gross photograph of a large teratocarcinoma containing various tissues In many areas the tumor was undifferentiated (W U neg. 49 282.)

Fig 623 —Photomicrograph of an area of adenocarcinoma in a teratocarcinoma. (Moderate enlargement.) (W U neg 47 744)

focal areas of malignant epithelial and stromal tissue. Friedman has an interesting hypothesis to explain metastases from an apparent adult teratoma. He proposes that undifferentiated areas occur early and metastasize to distant zones,



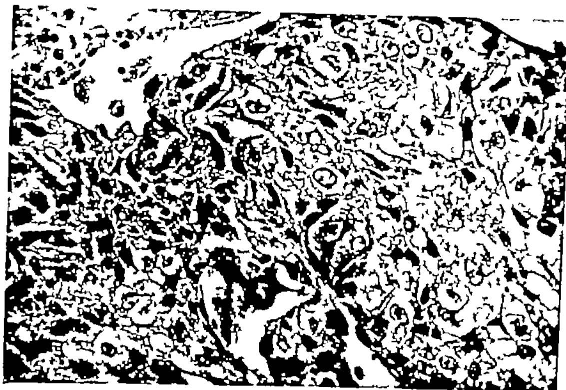


Fig 624—Hemorrhagic choriocarcinoma in a 35-year-old man. Extensive metastases were present when the tumor was discovered (Courtesy Dr Franz Leidler Veterans Hospital Jefferson Barracks Mo.)

Fig. 625—Photomicrograph of the choriocarcinoma shown in Fig 624 Note the blending of syncytial and cytotrophoblasts. (×400) (W U neg 52-4342.)

then undergo maturation so that several years later only adult type of tissue is found. In order to substantiate such a hypothesis it would be necessary to section serially an adult teratoma having metastases in order to avoid overlooking minute undifferentiated zones (Fig 623)

Embryonal Carcinoma (Monodermal Teratoma)

Embryonal carcinoma unfortunately makes up a rather high percentage of all testicular tumors This neoplasm is often large and grossly is variegated Microscopically it is highly undifferentiated only occasionally forming glands The variation of this pattern helps to make the diagnosis

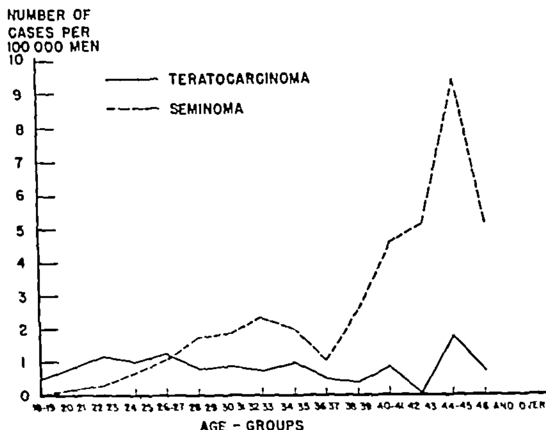


Fig. 626 —This graph shows the increased incidence of seminoma in older age groups. (W U neg 49-3597) (From Friedman, N B., and Moore R. A. Mil Surgeon 99: 573 1946.)

Choriocarcinoma

Choriocarcinomas are very malignant tumors, which account for about 5 per cent of testicular tumors. These neoplasms are often small there may be no enlargement of the testis They are usually hemorrhagic and partially necrotic (Fig 624) Rarely the primary tumor may completely regress, leaving only a scar containing hemosiderin pigment (Laipply) Microscopically these tumors have giant trophoblastic cells with large atypical nuclei and cytotrophoblasts (Fig 625)

Seminoma (Embryonal Carcinoma)

The seminoma is a distinctive neoplasm, making up 30 to 40 per cent of all testicular tumors (Fig 626) Grossly it usually is of moderate size, homogeneous light yellow and may show zones of necrosis (Fig 627) Microscopically the individual cells are uniform with prominent nuclei and prominent nucleoli (Figs.

628 and 629) Lymphatic infiltration may or may not be present. Areas of peculiar granulomatous material with giant cells forming pseudotubercles may be present as in the dysgerminoma. The origin of the seminoma is uncertain, but Willis believes it arises from seminiferous tubules. In dogs tumors arising from seminiferous tubules are common, but are not associated with teratoid neoplasms as may occur in man.



Fig 627 —Typical homogeneous cellular seminoma containing areas of necrosis. (W U neg 52 1977)

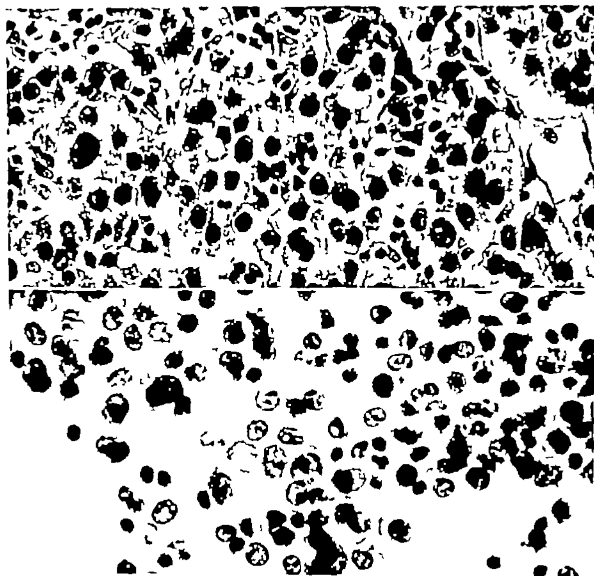
SPREAD

Testicular tumors spread first to iliac and periaortic lymph nodes. They do not involve the inguinal lymph nodes unless there is involvement of the skin of the scrotum or the tumor recurs in a cutaneous scar The adult type of teratoma may or may not metastasize. The embryonal carcinoma frequently metastasizes early and the choriocarcinoma almost always has widespread metastases by the time the tumor is diagnosed. Distant metastases in testicular tumors are frequently found in the lung and may extend to supraclavicular lymph nodes.

CLINICOPATHOLOGIC CORRELATION

A malignant testicular tumor is accompanied by progressive painless enlargement of the testis. It may grow slowly or with appalling speed The choriocarcinoma may not be palpable but is frequently accompanied by signs of gyneco-

mastia large amounts of chorionic gonadotropin in the urine (Brewer), and large mediastinal masses The best treatment of testicular tumors has not been definitely established The choriocarcinoma is practically never cured, no matter what the treatment Seminoma is a radiosensitive and radiocurable neoplasm, the preferred treatment is surgical removal of the tumor with thorough irradiation of the retroperitoneal area whether there is clinical evidence of metastases or not High curability is possible in this tumor—80 per cent five year survival without involvement



Figs. 628 and 629 —Photomicrographs demonstrating a prepared microscopic section of a seminoma and a stained smear made from a fresh gross specimen. The undistorted seminoma cells have well-defined nuclei and nucleoli. Cytoplasm is abundant. (Fig 628 ×520 W U neg 50-5071 Fig 629 ×750 W U neg 52 2048)

of lymph nodes and 40 per cent five year survival with clinically involved lymph nodes. Surgical removal of all testicular tumors is indicated in order to determine the microscopic type of the tumor In the teratocarcinoma and the embryonal carcinoma cure is assured by surgical removal only if there are no distant metas

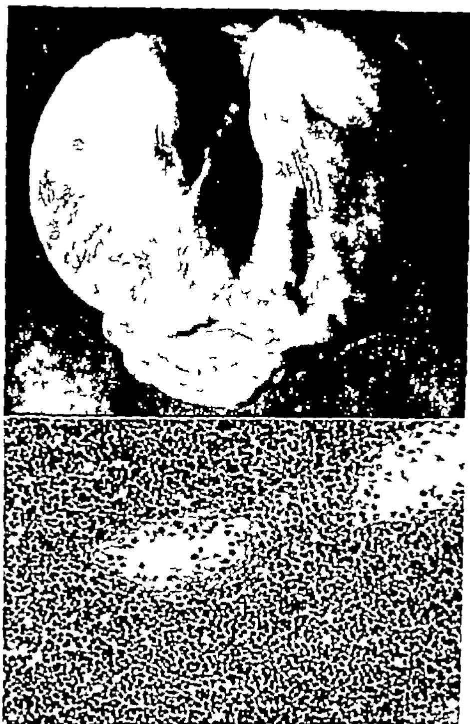


Fig 630 —Gross photograph of a lymphosarcoma completely replacing the testis. This lesion occurred in a male aged 47 there were no other clinical findings. (W U neg 52-4426.)

Fig. 631 —Photomicrograph of a lymphosarcoma of the testis. Note infiltration of lymphosarcoma cells between the atrophic tubules. (×225) (W U neg 51-5367)

tases. Irradiation is only rarely capable of sterilizing distant metastases in the periaortic area (Rusche Cox) Retroperitoneal lymph node dissection is ineffective except in rare instances since the operation is not a good en bloc dissection (Lewis) Certainly this operation is of no value if the nodes removed are negative it is of no value if all the nodes are positive for residual cancer undoubtedly remains. It is of possible value only if one or two lymph nodes are involved by tumor (Staubitz) Dixon has shown that a two-year freedom from evidence of recurrence after definitive treatment of a testicular tumor is evidence of cure in at least 90 per cent of instances



Fig 632 —Gross photograph of a firm grayish yellow lesion replacing testicular parenchyma in a young male A definite diagnosis of malignancy could not be made. The patient was well six years later We now believe the diagnosis to be granulomatous orchitis. (W U neg 52-4639)

RARE TUMORS AND LESIONS

Metastatic cancer of the testis is rare the lung and prostate were the most common primary sites in the group reported by Price We have also seen metastatic carcinoma from the prostate Primary lymphosarcoma of the testes (Dockerty Cohen) may be bilateral its cells grow between the tubules (Figs. 630 and 631)

We have seen a firm poorly defined yellowish mass in the testis of a young man. Microscopically the interpretation was difficult the diagnosis by various prominent pathologists included undifferentiated carcinoma seminoma, reticulum cell sarcoma Hodgkin s disease and granuloma. No treatment other than orchiectomy was undertaken The patient remains alive and well six years later We now believe that this is an example of granulomatous orchitis. These lesions may develop following trauma or possibly are an inflammatory reaction to disintegrated sperm (Spjut) The Sertoli cells are possibly precursors of the epithelioid elements of the granuloma (Fig 632)

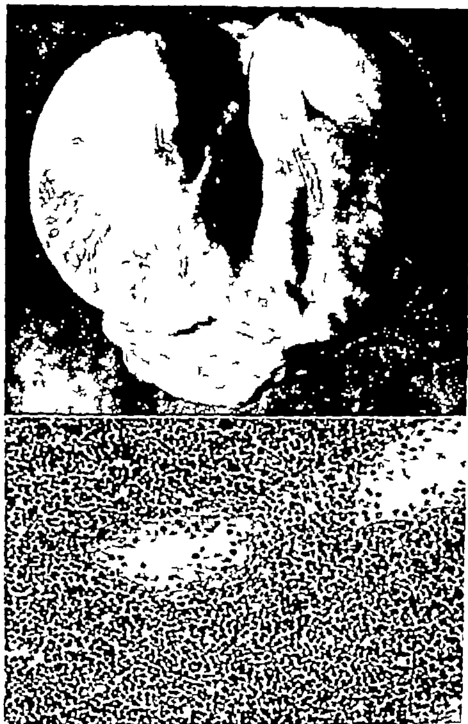


Fig 630.—Gross photograph of a lymphosarcoma completely replacing the testis. This lesion occurred in a male aged 47 there were no other clinical findings. (W U neg. 52-4496)

Fig 631—Photomicrograph of a lymphosarcoma of the testis. Note infiltration of lymphosarcoma cells between the atrophic tubules. (×225) (W U neg. 51 3367)

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EPIDIDYMIS AND SPERMATIC CORD

GRANULOMATOUS LESIONS
MESOTHELIOMA
RARE TUMORS
SPERMATIC CORD

GRANULOMATOUS LESIONS

Tuberculous infection of the epididymis is hematogenous in most instances with the process beginning in the interstitial tissue. Confluent caseation eventually involves the entire epididymis from which the testis may be secondarily infected (Fig 633) When the epididymis is involved through the blood stream, involvement of the ductus deferens is usually absent while the head is extensively involved. Conversely infection originating from the prostate causes extensive involvement of the ductus deferens and the tail of the epididymis (Auerbach)

Spermatic granulomas of the epididymis are probably due to damage to the epithelium and the basement membrane proceeding or following inflammation of the ducts. Probably the inciting cause is inflammation or trauma (Glassy) The granulomatous reaction may be related to an acid fast fraction of lipid from the sperm since this material can provoke a granulomatous reaction if injected subcutaneously in hamsters (Berg) The most frequent site of these lesions is in the superior pole they measure up to 3 cm in diameter Granulomatous reaction can be present without caseation. Epididymal ducts are often filled with masses of sperm.

True spermatoceles arise most commonly from the efferent ducts. These ducts are embedded in loose connective tissue rather than in smooth muscle. Such spermatoceles are lined with ciliated tall columnar cells similar to those in the ducts. Granulomatous inflammation, foreign body giant cell reaction and cholesterol clefts are common in such lesions

MESOTHELIOMA

A tumor of the epididymis designated as mesothelioma by Evans and Masson has been called adenomatoid tumor by Golden. In the past it had numerous other names such as lymphangioma, adenoma and adenocarcinoma Grade 1 This distinctive neoplasm arises from the epididymis testicular tunics and serosal surface of the uterine tube (Fig 634) The tumor usually causes no symptoms when it arises from the salpingeal serous surface The tumor produces mass and pain in the region of the testicle These neoplasms most frequently occur in the third or fourth decade of life. Grossly they appear encapsulated, are firm grayish white in

color and rarely contain small cysts. Their average size is about 2 cm. Microscopically they present diverse patterns and contain a variable amount of stroma. They may form solid cords of cells which suggest epithelial neoplasm. In other instances they show cystic spaces lined by flattened cells which may have a brush border (Masson) (Fig. 635). These cells frequently contain vacuoles which do not stain for fat (Golden) but may stain faintly or strongly for mucicarmine (Masson). Evans has demonstrated that the lining of the serous surface of the peritoneum may be continuous with the cells lining glandular structures in the tumors arising in the region of the fallopian tube. Microscopically these tumors do not have a true capsule but, as far as is known, they do not locally recur or distantly metastasize. We favor origin from mesothelium (Fajers).



Fig. 633. Gross photograph of tuberculosis of the epididymis with confluent caseous masses. The testis is atrophic. (W U neg 49-6173.)

RARE TUMORS

A *leiomyoma* was reported by Spivack and a possible *fibrosarcoma* by Lazarus. Scalfi collected 58 *primary tumors* of the epididymis. Sherrick reported a *papillary cystadenoma* of the epididymis.

SPERMATIC CORD

Thompson emphasized that *lipomas* of the spermatic cord may become very large. The majority are benign. The lipoma forms in the serous fat around the margin of the internal inguinal ring and follows the spermatic cord. True lipomas are surrounded by tunica vaginalis and derive their blood supply from the vessels of the cord. Frequently there is an associated inguinal hernia. *Fibromas* occur about one-third as frequently as lipomas; true *myxomas* are rare. *Smooth muscle tumors* of the cord probably arise from the cremasteric fascia of the tunica vaginalis

(Hinman) *Dermoid cysts* of the spermatic cord have been reported. Rarely *sarcomas* occur in the spermatic cord particularly fibrosarcomas. We have seen two *malignant mesenchymomas*



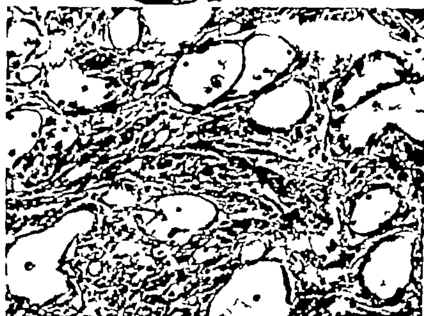


Fig 634 —Gross photograph of a typical mesothelioma of the epididymis. It is small, encapsulated, and about 2 cm. in its greatest diameter (W U neg 49-6449)

Fig 635 —Photomicrograph of typical mesothelioma with cystic spaces lined by flattened cells. (Moderate enlargement.) (W U neg 49-1518)

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PENIS

NONNEOPLASTIC DISEASES
ERYTHROPLASIA OF QUEYRAT (EPIDERMOID CARCINOMA IN SITU)
CARCINOMA

NONNEOPLASTIC DISEASES

Inflammatory lesions of the penis are rarely biopsied. A *chancre* is a chronic inflammatory process which may be granulomatous. *Condyloma acuminatum* of the penis is a nonvenereal disease of virus origin. The lesions occur in the moist coronal sulcus. Microscopically they show complicated papillary infolding of squamous epithelium (Fig 636). Plastic induration of the penis (*Peyronie's disease*) is a circumscribed fibrous thickening of the tunica albuginea of the penis occurring usually after the age of 40. Microscopically it is hyalinized fibrous tissue containing at times cartilage and bone. It begins on the dorsal surface (Schourup) between the septa of the corpora cavernosa but does not involve them. It may be associated with Dupuytren's contracture. It may be cured with small amounts of irradiation or by excision (Lowsley). *Balanitis xerotica obliterans* is described in the section on Nonneoplastic Conditions of the Skin (see p 46).

ERYTHROPLASIA OF QUEYRAT (EPIDERMOID CARCINOMA IN SITU)

Erythroplasia of Queyrat is a rare lesion of the penis usually described as a well-defined, bright red plaque with a shiny moist surface (Sulzberger) (Fig 637). Microscopically it is epidermoid carcinoma in situ; rarely it progresses after a long time to invasive carcinoma. It can be confused with three other lesions: exudative discoid and lichenoid chronic dermatosis (Sulzberger), lichen planus and psoriasis. Exudative discoid and lichenoid chronic dermatosis is a nonspecific process of unknown etiology. Lichen planus and psoriasis are not difficult to diagnose microscopically. Invariably lesions occur elsewhere. Surgical excision of erythroplasia of Queyrat is the treatment of choice (Savatard).

CARCINOMA

Carcinoma of the penis is a relatively infrequent neoplasm in this country but is common in Asia (Chu). If circumcision is done shortly after birth carcinoma practically never develops. If circumcision is delayed until the age of 10 as is the Moslem custom, carcinoma is more likely to develop. Carcinoma of the penis is conspicuously frequent in young Negro males (Lenowitz). It is possible that carcinoma is related to personal hygiene and the carcinogenic effect of the



Fig 636 —Photomicrograph of condyloma acuminatum with complicated papillary infolding of well-differentiated squamous epithelium. Basement membrane is intact (Low power) (W U neg 50-477)



Fig 637 – Erythroplasia of Queyrat (epidermoid carcinoma in situ) of the penis. This lesion had been present for a considerable time period. Changes seen microscopically in all sections did not violate the basement membrane (W U neg 51 ?073)

PENIS

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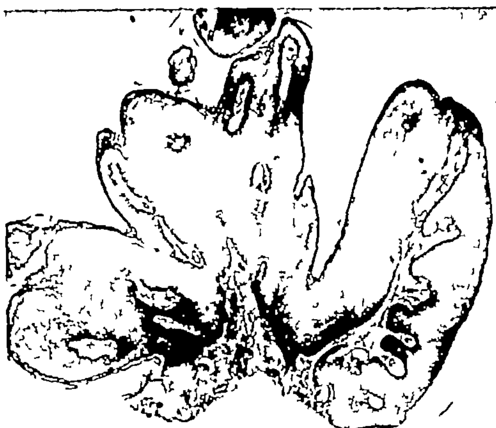


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Fig 638 —Gross photograph of an extensive verrucous squamous carcinoma. This tumor occurred in a 79-year-old man and there were no metastases. (Courtesy Dr Richard Johnson Ellis Fischel State Cancer Hospital Columbia, Mo.)

Fig 639 —Cross section of the large tumor shown in Fig 638 demonstrates its failure to involve the urethra. (Courtesy Dr Richard Johnson Ellis Fischel State Cancer Hospital, Columbia Mo)



Fig 640 —Clinical photograph of ulcerating undifferentiated carcinoma of the penis. Metastases were present in the inguinal lymph nodes. (W U neg 52 3969)

smegma bacillus These factors would be enhanced by failure to circumcise. Grossly carcinoma of the penis has primarily two forms It may develop as a papillary verrucoid mass or as an ulcerating lesion Lesions of the prepuce tend to infiltrate, while those of the glans fungate (Bassett)

The *verrucoid* type grows to be a large polypoid tumor which may replace the penis. It rarely metastasizes in spite of its large size (Figs. 638 and 639) Microscopically it is an extremely well-differentiated papillary squamous tumor having the same pattern as verrucous squamous carcinoma of the buccal mucosa. Local excision is the only treatment necessary

The *ulcerating* variety begins on the glans and eventually destroys it (Fig 640) It may metastasize to the inguinal lymph nodes invade the urethra and involve distant lymph nodes. It is rather poorly differentiated If the tumor has invaded the corpora cavernosa or urethra, distant metastases are more probable Local excision followed by bilateral inguinal node dissection is the recommended treatment.

Carcinoma either squamous or transitional may arise primarily in the male urethra. It may follow stricture produced by trauma or gonorrhea. It is most common in the bulbomembranous portion (Vernon)

Carcinoma of the penis is best treated by amputation, local recurrence is rare. This tumor metastasizes to the inguinal lymph node area. Because of infection associated with the carcinoma enlargement of these nodes almost invariably takes place so that the clinical appraisal is extremely inaccurate. If metastases are present practically no cases are cured (Bassett) Secondary involvement of the penis by cancer can occur directly or by retrograde lymphatic and venous extension (Paquin)

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Chapter 17

FEMALE REPRODUCTIVE SYSTEM

VULVA
VAGINA
UTERUS—CERVIX
UTERUS—ENDOMETRIUM
UTERUS—MYOMETRIUM
FALLOPIAN TUBES
OVARY
PLACENTA

VULVA

LYMPHOPATHIA VENEREUM CHONDYLOMA ACUMINATUM
LEUKOPLAKIA AND KRAUROSIS
TUMORS
- **Hidradenoma and Paget's Disease**
- ***Epidermoid Carcinoma in Situ***
- **Epidermoid Carcinoma, Invasive**
- **Malignant Melanoma**
- **Clinicopathologic Correlation**
- **Carcinoma of the Urethra (Rare Neoplasms)**

LYMPHOPATHIA VENEREUM CONDYLOMA ACUMINATUM

Lymphopathia venereum is a virus disease which may extensively involve the vulva and extend into the vagina. The Frei test is specific. The perirectal tissue also may *be involved (Fig 447) Taussig reported eleven patients with vestibular* carcinoma, nine of whom had a previous history of lymphopathia venereum in *this zone. Inflammatory conditions of the vulva are infrequent.* In condyloma acuminatum soft multiple papillary masses are formed this disease is often associated with but not necessarily related to other venereal diseases. We have not seen these lesions become malignant. Microscopic examination shows a complicated papillary arrangement of well-differentiated squamous epithelium. The basement membrane is intact (Fig 641)

LEUKOPLAKIA AND KRAUROSIS

After the menopause kraurosis (shrinking) and atrophy of the vulva may occur Lichen sclerosus et atrophicus is synonymous with kraurosis (see p 46 Skin) It is not precancerous and must be differentiated from leukoplakia (Streitmann) Other synonyms for this condition include leukoplakic vulvitis of the atrophic type and sclerosing atrophy (Figs 612 and 613) True precancerous leukoplakia occurs as superficial grayish white patches. It may be extensive or localized and can extend to the perianal region Microscopically hyperkeratosis variable degrees of hyperplasia and dyskeratosis are associated with chronic inflammation About 25 per cent of carcinomas of the vulva are associated with leukoplakia. If leukoplakia is limited local excision may be sufficient. If it is extensive vulvectomy is indicated Lichen sclerosus and leukoplakia can both be present (Clark)



Fig 641 —Photomicrograph of condylomata acuminata with a complicated papillary arrangement of well-differentiated squamous cells with an intact basement membrane. (Low power) (W U neg 52 2478)

TUMORS

Hidradenoma and Paget's Disease

Benign sweat gland tumors of the vulva are called hidradenomas. These tumors arise on the labia majora, are rarely larger than 1 cm. often have been present for a long time are well circumscribed, and usually are considered clinically as sebaceous cysts (Anderson) Rarely they ulcerate through the skin and simulate carcinoma. Microscopically they have a rather complicated papillary pattern

They apparently arise from double-layered apocrine glands (Figs. 644 and 645). These tumors are benign (Danforth). Double layering is present.

Paget's disease of the vulva is analogous to Paget's disease of the breast. *Most* authorities believe it arises within apocrine glands and grows upward to infiltrate the skin surface. Tumor cells in the glands and in the epidermis stain positively for epithelial mucin (Paget).

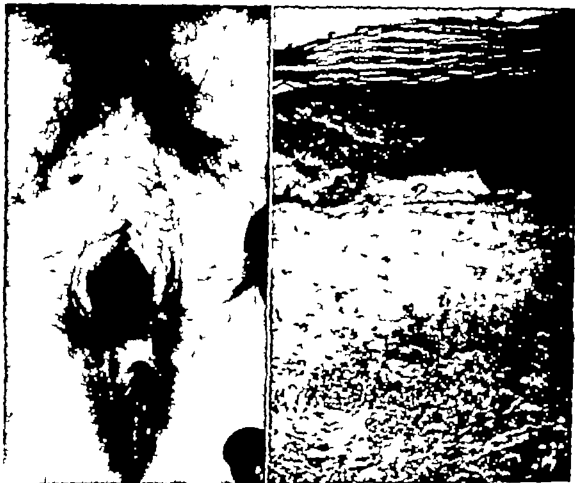


Fig. 642.—Clinical photograph of kraurosis (lichen sclerosus atrophicans) of the vulva. Note shrinkage and atrophy. (EFSCH 85-0.)

Fig. 643.—Photomicrograph of kraurosis of the vulva with hyperkeratosis atrophy and bandlike arrangement of collagen in the dermis. (×125.) (W.U. neg. 50-3746.)

Epidermoid Carcinoma in Situ

Epidermoid carcinoma in situ is a rare plaquelike lesion of the vulva which is slightly elevated, grayish pink, and has well-defined margins (Gonin; Jeffcoate) (Fig. 646). This vulvar lesion is identical with the penile lesion, erythroplasia of Queyrat (see p. 602, Penis). Clinically it is usually not diagnosed because of its long duration and its resemblance to infection. Biopsy shows the classical changes of carcinoma in situ. This lesion should be excised because in time it may become invasive carcinoma.



Fig. 644 —Photomicrograph of a typical hydradenoma of the vulva. Note apparent en capsulation and papillary pattern. (Low power) (W U neg 52 2045)

Fig 645 —At higher magnification the double layer of cells and the characteristic cellu lar pattern can be seen. Note evidence of active secretion substantiating origin from apocrine type glands. (×440) (W U neg 52 2047)

Epidermoid Carcinoma, Invasive

Invasive carcinoma of the vulva frequently is associated with leukoplakia. It begins usually on the labia majora but may arise on the labia minora or even in the region of the clitoris. This tumor grows rather slowly ulcerates and eventually spreads widely (Fig 647) Microscopically it usually is a well-differentiated squamous carcinoma. Epidermoid carcinoma in situ occurs frequently at the margins of invasive carcinoma (Fig 648) In the region of the clitoris it may be undifferentiated. Carcinoma which arises from the labium spreads to inguinal



Fig 646—Clinical photograph of carcinoma in situ involving a wide area of the vulva as an elevated plaque. (W U neg 52 2102.) (From Gonin R. Dermatologica 92 74 1946)

lymph nodes. As this tumor is invariably infected the regional nodes enlarge. It is impossible to predict whether the nodes are enlarged because of cancer or infection. If the carcinoma is in the region of the clitoris, it may spread directly to deep nodes. The treatment of choice is radical vulvectomy followed by radical bilateral inguinal lymph node dissection.

Malignant Melanoma

Malignant melanoma of the vulva may arise from a pre-existing junctional nevus. In 27 consecutive moles of the vulva seen at Washington University School of Medicine only 6 showed junctional activity and all of these were compound in type (see Skin) Moles of the vulva should probably be removed prophylacti

cally Malignant melanoma is the second most common malignant tumor o organ although it is much less frequent than epidermoid carcinoma. Malig change in a mole is accompanied by deepening pigmentation, increased gr rate and ulceration The microscopic pattern is similar to malignant mela of the skin (see Skin) The treatment of choice is radical vulvectomy wi lateral inguinal lymph node dissection Practically no cases are cured



Fig 617—Clinical photograph of a large ulcerating carcinoma of the vulva with leuk (EFSCH 11,929) (Courtesy Dr Richard Johnson.)

Clinicopathologic Correlation

The aggressive treatment of leukoplakia and lymphopathia venereum vulva may prevent some carcinomas The surgical treatment of carcinoma i cal vulvectomy with bilateral radical inguinal lymph node dissection. In tients who had this form of therapy, 29 survived without evidence of diseas three and one half years to five or more years 19 survived five or more (Green) Prophylactic removal of moles from the vulva may prevent ma melanoma. When malignant melanoma is clinically obvious, no cures are to be obtained.

Carcinoma of the Urethra (Rare Neoplasms)

Carcinoma of the female urethra is included by some with the vulva because it occurs most commonly at the meatus at the junction of transitional and stratified squamous epithelium. Rarely it may be an adenocarcinoma (Brack) These tumors have a fair prognosis. The urethral caruncle occurring exclusively in the female urethra is not a true neoplasm. It has the appearance of a small raspberry, bleeds easily and may become infected. Microscopically extreme vascularity and complicated small nests of epithelium may cause it to be incorrectly diagnosed as malignant. These lesions often recur after excision (Palmer)



Fig 648.—Photomicrograph of epidermoid carcinoma in situ on the margin of an invasive carcinoma. Note disorganization of all layers with prominent variation in size and shape of cells but with an intact basement membrane. (×150) (W U neg 52 2477)

About 65 cases of *basal cell carcinoma* of the vulva have been reported (Siegler) These neoplasms should be excised. *Supernumerary breast tissue* may occur in the vulva and form tumors (Siegler) Fibromas, leiomyomas hemangiomas endometriosis, and granular cell myoblastoma (p 865) have been reported (Weinshel)

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VAGINA

BENIGN LESIONS
MALIGNANT TUMORS

BENIGN LESIONS

In adults the vagina is impervious to most infections. Rarely *lymphopathia venereum* may involve it. Benign tumors of the vagina are rare but can arise from any component. We have seen *fibroma hemangioma* and *leiomyoma*. *Gartner's duct cysts* are fairly common in the vagina and are usually present on the anterior



Fig. 649 —Gross photograph of an ulcerating carcinoma of the vagina which had infiltrated the rectovaginal septum. It was removed by pelvic evisceration. (W U neg. 50-2111)

lateral or lateral vaginal wall This duct is the vestigial remnant of the Wolffian duct The cysts are lined by low cuboidal cells without cilia We have seen two carcinomas arising within such cysts They have a distinctive microscopic pattern and unlike cervical adenocarcinomas do not form mucin

MALIGNANT TUMORS

Epidermoid carcinoma arising primarily in the vagina is a rare neoplasm Most of these tumors represent extension from the cervix. In order to make a diagnosis, the lesion must be clearly separated from the cervix (Figs 649 and 650)



Fig 650 —Photomicrograph of sarcoma botryoides of the vagina with a polypoid configuration and intact overlying epithelium. (Low power) (W U neg 51 154) (Slide contributed by Dr Howard Ulfelder Boston, Mass.)

Sarcoma botryoides is a rare polypoid slowly growing invasive tumor usually occurring in infancy and arising from the vagina just below the mucosa (Fig 650) It is made up of myxomatous tissue and is often highly undifferentiated. Tumor cells with cross striations are common. These tumors cause death by *direct extension* rather than by distant metastases (McFarland) Ulfelder radically removed a sarcoma of this type from a 22 month-old child He removed the vagina and uterus but was able to spare the ovaries and both tubes. The child has now survived over five years without evidence of recurrence or distant metastases. Tumors of this nature occur in other organs At the Armed Forces Institute of Pathology 11 cases have been reported 4 of the vagina, 5 of the bladder and 1 of the anus and cervix. Only 2 of them metastasized (Ober)

The vagina is frequently involved by primary carcinoma of the cervix. Carcinoma of the rectum occasionally invades the wall of the vagina and ulcerates its surface. Carcinoma of the endometrium is particularly prone to metastasize to the submucosa of the vagina. We have seen one instance of primary melanocarcinoma of the vagina.

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UTERUS—CERVIX

CHRONIC CERVICITIS, NABOTHIAN CYSTS, AND POLYPS

Chronic cervicitis, nabothian cysts and polyps of the cervix are probably expressions of inflammation The biopsies of cervices of adult females all show some degree of chronic inflammation. Retention nabothian cysts develop with block of the cervical glands. They appear grossly as cystic spaces filled with mucoid material The cervical polyp may be small or several centimeters in diameter On cut surface there are cystic spaces. Microscopically the surface may be covered with squamous epithelium. Areas of epidermization are frequent. Such polyps are not true neoplasms We have not seen carcinoma develop in a cervical polyp Hertig found 5 carcinomas in situ in 1 600 polyps thus demonstrating that polyps are no more or less potentially malignant than the cervix as a whole.

DECIDUAL REACTION

Decidual reaction in the cervix during pregnancy may be confused with carcinoma. These lesions are multiple small yellowish or red elevations of the cervical mucosa they are soft friable, and bleed easily with trauma. Rarely these processes may be transformed into fungating masses difficult to distinguish from carcinoma (Bausch) Microscopically the diagnosis should not be difficult (Fig 651)

EPIDERMOID CARCINOMA IN SITU

Intraepidermal or noninvasive carcinoma of the cervix has been designated as epidermoid carcinoma in situ. Invasive squamous carcinoma arises predominantly in the endocervix at the squamocolumnar junction an area where carcinoma in situ also begins (Howard) (Fig 652) Carcinoma in situ was well described by Schottlaender in 1912 The incidence of this entity is influenced greatly by the liberality of the pathologist in diagnosing it and also by the selection of material Figures quoted on incidence often come from gynecologic clinics where pa



Fig 651.—Photomicrograph of decidual reaction in the cervix. Note the large decidual cells growing diffusely through the cervix. *Clinically this patient was thought to have early* carcinoma of the cervix. (×220.) (W U neg 50-2839.)



Fig 652.—Photomicrograph of squamocolumnar junction in the endocervix, a frequent site of origin for carcinoma in situ. (Low power.) (W U neg 56-747.)

tients enter with signs and symptoms of some gynecologic abnormality *Howard* studied 400 uteri removed for noncervical disease 14 cases of carcinoma in situ and 7 with atypical changes were found Of these 400 uteri, 98 per cent showed evidence of inflammation 75 per cent *had nabothian cysts and 83 per cent had* endocervical metaplasia

The microscopic changes which allow this diagnosis often occur abruptly (Te Linde) and consist of increased basal cell activity, hyperplasia of the epithelium distortion of the architectural pattern and of most importance prominent variations in the size and shape of cells with numerous mitotic figures There is an increase in the size of the nucleus relative to the volume of cytoplasm When these changes *involve all layers* we believe the diagnosis of carcinoma in situ is justified (Fig 653) The periodic acid Schiff stain (McManus) shows no cellular glycogen in carcinoma in situ There appears to be little doubt that when such changes occur progression to invasive carcinoma eventually develops. The length of time required is not known but on the basis of cases reported five or more years is necessary With continued extension of the process *carcinoma in situ involves* cervical glands and may be incorrectly called *invasive carcinoma* (Fig 654) We do not call these lesions invasive unless they extend beyond the basement membrane and infiltrate the fibromuscular stroma of the cervix. *Spread of carcinoma in situ over* endocervix and vagina can occur (Foote), we have seen one case involve the entire endometrium the fallopian tubes and the vagina to the introitus There is little *doubt that carcinoma in situ extends more often up the canal than down on the* portio (Gusberg) In numerous instances biopsy showing carcinoma in situ represents the peripheral manifestations of a truly invasive carcinoma which is diagnosed *only by endocervical curettement True carcinoma in situ of the cervix* usually occurs at an earlier age (average age, 36 6 years Pund) than does invasive carcinoma (average age 48 6 years) There is no doubt that this lesion has often been diagnosed incorrectly and radical therapeutic measures instituted *(Novak)* Squamous metaplasia particularly associated with infection is confusing (Fig 655) In pregnancy confusing changes occur which may be diagnosed incorrectly as carcinoma. These changes include pseudopolyps squamous metaplasia, and decidual reaction. In addition true invasive carcinoma can be present Carcinoma in situ has been reported in pregnancy which completely regressed after pregnancy (Fig 656) We believe such cases are extremely few *in number Basal cell hyper*activity occurs in pregnancy and may be diagnosed incorrectly as carcinoma in situ this lesion of course may progress to invasive carcinoma or it may be reversible We believe that if strict criteria of *carcinoma in situ are followed this diag*nosis will be made only rarely in pregnant patients (Danforth) Hamperl made a thorough study of this problem by biopsying the cervix in 361 pregnant women. He found 9 cases of carcinoma in situ which *persisted after termination of the* pregnancy Carter described 38 patients who showed changes in the cervix interpreted as marked cytologic atypia In spite of these changes, 11 of these patients had children (23) and none of them *had developed invasive cancer at the* time of the report. This would seem to indicate that under certain circumstances a patient with a diagnosis of carcinoma in situ can risk childbearing

Exfoliative Cytology

Exfoliative cytology as a screening procedure may be justified for patients without symptoms. In a study made by Erickson of 108 000 women over 20 years of age 393 *intraepithelial carcinomas* were found of which 353 (90 per cent) had

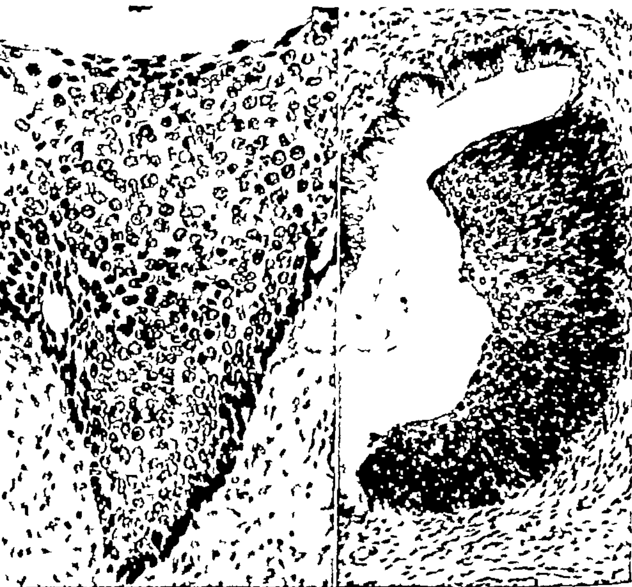


Fig 653 —Photomicrograph of epidermoid carcinoma in situ with hyperplasia of the epithelium, disturbance of architecture in all layers, and many mitotic figures. (×390.) (W U neg 50-3763)

Fig 654 —Photomicrograph of the tumor shown in Fig 653 with extension of the process to involve a cervical gland. (×250) (W U neg 50-3762)

not been suspected 373 invasive cancers of the uterus were found of which 112 (30 per cent) were not suspected. These figures show clearly the value of this somewhat expensive, time-consuming procedure as a method for the early detection of cancer "On the second examination of 33 000 women 2 2 with intraepithelial carcinomas were found per thousand, as compared with 3 6 on the first examination while the



Fig 655—Photomicrograph of extensive squamous metaplasia of the cervix. The individual cells are uniform, and there is considerable inflammation. This type of lesion often is incorrectly diagnosed as carcinoma. (×180) (W U neg 50-3947)

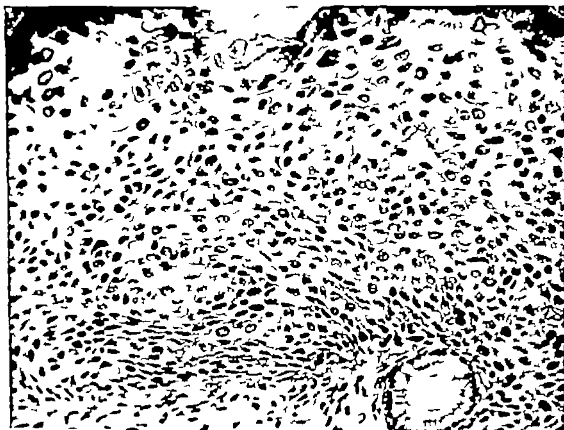


Fig 656—Photomicrograph of changes occurring in the pregnant uterine cervix which are difficult to distinguish from true carcinoma in situ. This lesion completely regressed after the termination of pregnancy (×360) (W U neg 51 1953) (Slide contributed by Dr J Schleifstein.)

rate for invasive cancer was reduced from 3 4 to 0 3 cases per thousand women. These changes are related to the natural history of cancer" (Erickson)

Routine exfoliative cytology is certainly indicated in all patients seen by the gynecologist for in this group the percentage of unsuspected early cancer will be much higher than in the group without symptoms. If cells are found that are atypical or thought to be cancer this is *not* an indication for therapy but an indication for investigation (biopsy or endocervical curettement) In certain patients in whom a definite diagnosis of carcinoma in situ is made exfoliative cytology may be useful for follow up After radiation therapy cytology may be used to demonstrate evidence of postirradiation persistence. The interpretation of such vaginal smears may be extremely difficult Kohn diagnosed 5 cases of local recrudescence by the vaginal smear method. She emphasized that the collected cells represented the entire cell population of the vagina and cervix, and therefore was more accurate than a biopsy taken from a small limited area

Clinicopathologic Correlation

What should be the pathologist's attitude toward the diagnosis of carcinoma in situ and what advice should he give the clinician? First, the criteria for the diagnosis should be strict. The pathologist should be particularly careful in the interpretation of biopsies from pregnant women Before the diagnosis is made a cold knife endocervical curettement is necessary to rule out invasive carcinoma Fennell believes that if biopsies are done the minimum should include the squamous columnar junction at four different points and curettage of the endocervical canal. If invasive carcinoma is absent in the curetted tissue it will practically never be found by subserially sectioning the removed cervix Local conization or amputation of the cervix may then be sufficient treatment. Radical surgery or removal of the uterus with ovarian preservation may be excessive in the young woman in the postmenopausal group such treatment is indicated Conservatism *may be warranted in young married women because of the time lapse between in situ change and invasive cancer* Exfoliative cytology is extremely helpful in following patients who have had conservative treatment

EPIDERMOID CARCINOMA

Invasive squamous carcinoma of the cervix is the commonest malignant tumor of the gynecologic tract. It appears most often in the upper age groups, but is common in patients under 40 There is a low incidence in Jewish women. Evidence exists supporting the association of early marriage, multiparity low economic levels of existence and possibly syphilis with a high incidence of cervical carcinoma. Carcinoma of the cervix has an extremely low incidence in nuns (Gagnon)

Grossly carcinoma may grow out of or may infiltrate the cervix. The bulky carcinomas which grow out of the cervix are less likely to invade surrounding structures than are the infiltrating ones Carcinoma of the cervix is usually an undifferentiated squamous carcinoma forming plexiform masses (Fig 657) Only rarely is it highly keratinized or so poorly differentiated that tumor giant cells are prominent (Fig 658)

The primary treatment of invasive carcinoma of the cervix is radium and external pelvic irradiation. This treatment cures the majority of the earlier stages of cervical cancer. When carcinoma is found to persist locally after irradiation therapy, pelvic exenteration should be seriously considered because a considerable number of these patients will have the persistent tumor confined to the pelvis. This operation removes all pelvic viscera and lateral pelvic lymph node bearing



Fig. 657. Photomicrograph of a typical squamous carcinoma of the cervix with plexiform masses. (×127.) (W.U. neg. 50-5760.)

Fig. 658.—Photomicrograph of a highly undifferentiated squamous carcinoma of the cervix. This has a sarcoma-like appearance with many tumor giant cells and bizarre mitotic figures. (×600.) (W.U. neg. 52-592.)

tissue (Fig 659) At laparotomy the surgeon should carefully examine the upper abdomen particularly the periaortic area for evidence of spread outside the pelvis. Any suspicious lymph nodes or liver nodules should be submitted to the pathologist for frozen section before the operative procedure is begun Gross appraisal of enlarged extrapelvic nodes is unreliable The study of the surgical specimen should



Fig 659—Gross photograph of a specimen from a pelvic exenteration done by Dr Eugene Bricker St Louis Mo. The specimen has been so sectioned that the intimate relation between bladder cervix, vagina and large bowel can be seen. There was persistent carcinoma in the cervix with invasion of the right parametrium. There were no involved lymph nodes of thirty examined. (W U neg 51-699)

include a careful examination of the lymph nodes, the lateral edges of the resection and the local extent of the tumor Microscopically the nodes, vessels, and adjacent organs should be examined for evidence of tumor Other indications for pelvic exenteration are occasionally carcinoma of the rectum, severe pelvic irradiation necrosis, and recurrent carcinoma of the endometrium. The five year survival rate for patients undergoing this formidable procedure for postirradiation persistent carcinoma of the cervix is approximately 25 per cent (Bricker)

ADENOCARCINOMA

Adenocarcinomas make up about 5 per cent of all carcinomas of the cervix, this percentage is higher in Jewish women (Gusberg) The tumor presents no differentiating gross characteristics Microscopically well-differentiated glands



Fig 660 —Photomicrograph of well-differentiated mucin-secreting adenocarcinoma of the cervix. (×360) (W U neg 50-5074)

Fig 661 —Extremely well-differentiated adenocarcinoma of the cervix. Note stratification of cells with loss of nuclear polarity (×440) (W U neg 52 1832)

have the characteristics of cervical mucus-secreting epithelium (Fig 660) We have seen several tumors in which excellent differentiation made the diagnosis of carcinoma quite difficult (Fig 661) Carcinomas of the endometrium, ovary

and even carcinomas of the gall bladder and breast may metastasize to the cervix and be called primary The clinical findings may make this mistake avoidable. Carcinomas of the endometrium usually produce no mucin and resemble endometrial glands Carcinomas of the ovary often have secondary papillary projections. On this basis we have diagnosed carcinoma of the ovary invading the cervix in two patients, both diagnoses were later shown to be correct. There is no difference in the response of epidermoid carcinoma and adenocarcinoma to irradiation therapy Rare adenocarcinomas of mesonephric origin have been reported (Mackles)

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and even carcinomas of the gall bladder and breast may metastasize to the cervix and be called primary. The clinical findings may make this mistake avoidable. Carcinomas of the endometrium usually produce no mucin and resemble endometrial glands. Carcinomas of the ovary often have secondary papillary projections. On this basis we have diagnosed carcinoma of the ovary invading the cervix in two patients; both diagnoses were later shown to be correct. There is no difference in the response of epidermoid carcinoma and adenocarcinoma to irradiation therapy. Rare adenocarcinomas of mesonephric origin have been reported (Mackles).

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UTERUS—ENDOMETRIUM

ENDOMETRIOSIS; ADENOMYOSIS

CYCLIC CHANGE

TUMORS

- Carcinoma
- Sarcoma
- Mesodermal Mixed Tumors

ENDOMETRIOSIS, ADENOMYOSIS

The theories of the production of endometriosis are innumerable. Probably endometriosis results from a combination of factors rather than a single cause. Those factors would include myometrial extension implantation, and lymphatic or hematogenous metastases. Javert* has summarized the available methods of the spread of endometrial tissue as follows

1 Direct myometrial extension	Schatz (1884) Baraban (1891) Pilliet (1894) Cullen (1896)
2. Congenital theories Müllerian Wolffian-cell rests	Cullen (1908) v Recklinghausen (1896)
3 Serosal metaplasia	Iwanoff (1896) Meyer (1903) Novak (1931)
4 Implantation theory	Sampson (1922)
5 Lymphatic metastasis	Sampson (1922) Halban (1924) Javert (1948)
6. Hematogenous metastasis	Sampson (1924)
7 Analogy to endometrial carcinoma	Sampson (1925)

This endometrium directly invades the myometrium and grows along lymph and blood vessels (Sampson) Coelomic metaplasia also occurs (Novak) Corner has reported nine cases suggesting origin of endometriosis from germinal epithelial elements. Implantation certainly occurs Sampson explained this on the basis of regurgitation and implantation of menstrual endometrium. Misplaced endometrium has been seen in the vagina, vulva bladder large bowel, small bowel, abdominal incisions, kidney lung groin and even in various skeletal muscles (Javert) Endometriosis in the vagina, vulva, and perineal and abdominal scars is related to previous operations (Tornquist) Hysterosalpingography can cause some cases of ovarian and peritoneal endometriosis (Teilum)

*Javert, C. J Cancer 2: 399-410 1949

By definition adenomyosis is the heterotopic occurrence of islands of endometrium in the myometrium (Brines) The term endometriosis should be reserved for heterotopic endometrium situated outside the uterus Endometriosis may occur without adenomyosis, this supports the theory of coelomic metaplasia. Grossly the uterus with adenomyosis is slightly enlarged At times the diagnosis may be made grossly because of dark brown cystic lesions in the wall (Gold)



Fig 662.—Photomicrographs of the sequential endometrial changes during the normal menstrual cycle *A* Interval endometrium. Note small glands and lack of vascularity (×115) (W U neg 52 3608) *B* Secretory endometrium Note saw-tooth epithelium, edematous stroma, and congested blood vessels. (×115) (W U neg 52 3609)

Microscopically the diagnosis of adenomyosis depends on the criteria used by the pathologist There is no submucosa in the endometrium the endometrium lies directly on the myometrium. It is not rare to see slight endometrial invagination this should not be diagnosed as adenomyosis With real muscular penetration the diagnosis becomes more certain the deeper the penetration. Only a small proportion of such lesions involve the outer third of the myometrium. The more superficial lesions usually communicate with the endometrial cavity (Brines) Basically adenomyosis is the presence of normal endometrial glands surrounded by stromal reaction. Frequently a hypertrophy of the muscle of the uterus is

closely associated with adenomyosis The endometrium and stroma reflect the changes of the menstrual cycle but bleeding is infrequent Rupture of the pregnant uterus can occur because of adenomyosis (Hertig)

Endolymphatic stromal myosis is a rare lesion representing proliferating stroma without glandular proliferation. In this condition the uterus contains one or more soft tumor masses which may locally extend into the broad ligaments, ovaries and tubes (Hunter) The tumor forms yellowish ropy or ball like masses in the lymphatics. Microscopically direct continuity can be demonstrated between the surface endometrium and the intramural tumor The tumor is within the lymphatics and reticulum surrounds each cell. This lesion is probably a low grade sarcoma but patients may live for long periods of time. In one of Hunter's 54 cases the lesion recurred locally over a 24 year period.

CYCLIC CHANGES

The ovulatory cycle is accompanied by changes in the endometrium which prepare it to receive the ovum. If the ovum is not fertilized, the proliferative endometrium is cast off by menstruation and the cycle repeats itself A normal endometrial cycle is associated with changes in both endometrium and stroma which usually allow the pathologist to diagnose microscopically the phase of the menstrual cycle (Table 26) (Fig 662)

TABLE 26 HISTOLOGY OF THE MENSTRUAL CYCLE*

DAY OF CYCLE	OVARY	ENDOMETRIAL PHASE	ENDOMETRIAL HISTOLOGY
1 to 4	Degenerating corpus luteum	Menstrual	Infiltration of leukocytes, degeneration and breakdown of endometrium hemorrhage and sloughing of endometrium
5 to 12	Developing follicle Mature follicle	Proliferative (estrogen)	Regeneration of endometrium from basalis glands rounded regular with piled-up cells mitoses stromal cells elongated spindly with scanty cytoplasm
13 to 15	Ovulation	Secretory (estrogen plus progesterone)	Glandular epithelium lines up in single layer, subnuclear vacuolization, followed soon by peripheral vacuolization of glandular epithelium with basal nuclei, glands tortuous, saw toothed stroma edematous in early stages, later stromal cells swollen, rounded, finally decidualike, congestion of blood vessels and infiltration of polymorphonuclears and lymphocytes in final stages

*From Schiller Walter The Female Genitalia. In Anderson, W A. D Pathology St Louis, 1948 The C V Mosby Co chap 40 p 1142.

The basal layer of the endometrium is not subject to the influence of progesterone Therefore, if biopsies are taken in the premenstrual phase for evidence of secretory activity (evidence of ovulation) and contain only the basal layer the diagnosis cannot be made. Furthermore the endometrium may show only patchy response to progesterone. Biopsies to determine an ovulatory phase should be taken preferably the first day of the menstrual period.

TUMORS

Carcinoma

Moss reviewed the common peculiarities of patients with adenocarcinoma of the endometrium They have a particular body build, are obese and have a high incidence of diabetes and hypertension Carcinoma of the endometrium is extremely rare after castration



Fig 663 —Gross photograph of a large polypoid benign endometrial polyp (W U neg 59 766)

Hertig reviewed cases of endometrial carcinoma in which there had been previous biopsies and showed that biopsies taken fifteen or more years before the recognition of cancer were normal while those obtained with less time lapse were abnormal. The sequence of events appears to be endometrial polyps, cystic or adenomatous hyperplasia, and anaplasia (Fig 663) He describes the changes of carcinoma in situ which consist of endometrial glands composed of large cells with abundant clear eosinophilic cytoplasm pale nuclei and slightly wrinkled nuclear membranes (Fig 664) The nuclei are arranged in irregular palisades The glands show no secretory activity nuclear pyknosis or cellular necrobiosis The in situ pattern in endometrial polyps occurs before the development of carcinoma.

Normal premenstrual endometrial glands show a similar staining reaction, but the nuclei are located slightly above the basement membrane and free cell margins are vacuolated and ragged. Eosinophilic glands are found in chronic endometritis, but other evidence of inflammation is present. Hertig felt that the presence of carcinoma in situ in endometrial glands was irreversible and that invasive carcinoma would eventually develop if the process was not removed. The other changes are not necessarily progressive. He demonstrated that focal carcinoma in situ is completely devoid of intracellular or intraluminal glycogen (Figs. 665 and 666). Younger patients (19 to 35 years of age) developing carcinoma of the endometrium frequently exhibit menorrhagia, sterility, amenorrhea, and obesity.

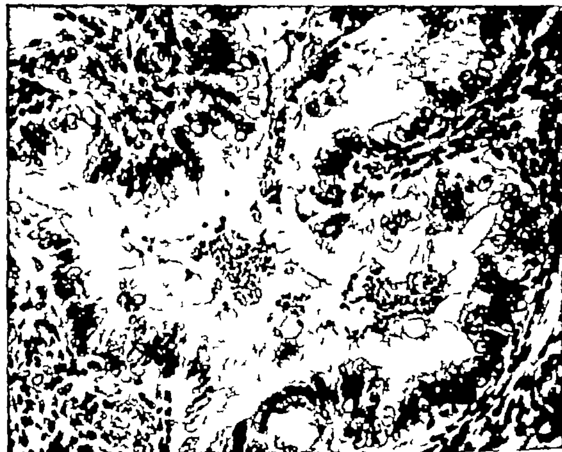


Fig. 664.—Photomicrograph of carcinoma in situ of the endometrium. The cells are large with abundant clear eosinophilic cytoplasm and some disorientation. These changes were focal in nature. (×320.) (W.U. neg. 52 2873.)

The ovaries of patients with carcinoma of the endometrium often showed ovarian cortical stromal hyperplasia. Most endometrial adenocarcinomas are fairly well differentiated. Occasionally they may present with very clear cells (Kay). Hertig mentioned that excess estrogen stimulation is thought to be causally related to endometrial carcinoma. Hertig reported that long continued pituitary stimulation of the uterus or ovary produced a period of prolonged and increased estrogen effect (apparently unopposed) which could result in carcinoma of the endometrium.

Grossly carcinoma of the endometrium may be present in a polyp, may grow diffusely, or form soft polypoid masses (Fig 667) At times it begins in a cornu and is missed by curettement By well planned irradiation therapy it is possible to sterilize the tumor in 3 out of 4 cases Of 70 patients treated by irradiation followed by hysterectomy and bilateral salpingo-oophorectomy, 62 were alive five years after treatment (Lampe)



Fig 665—Photomicrograph of an endometrium in a young woman with menstrual irregularities. The changes seen were thought to be atypical but not carcinoma. The date of curettement was Aug 27 1949 (×135) (W U neg 50-5076) (Slide contributed by Dr J P Wyatt St. Louis Mo.)

Fig 666.—Symptoms *continued and curettement on* July 26 1950 *demonstrated obvious carcinoma.* (×135) (W U neg 50-5077) (Slide contributed by Dr J P Wyatt, St. Louis Mo.)

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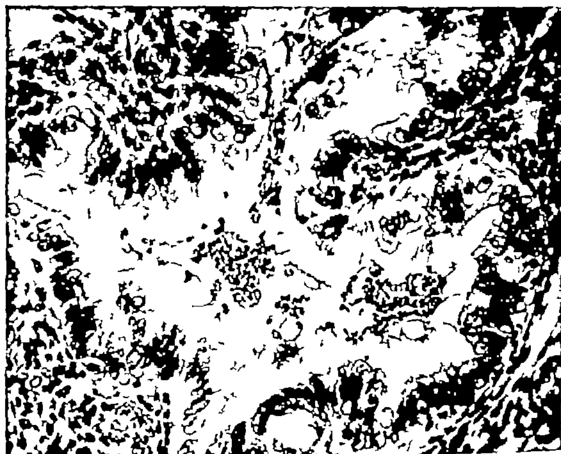


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Fig 666 —Symptoms continued and curettement on July 26 1950 demonstrated obvious carcinoma (×135) (W U neg 50-5077) (Slide contributed by Dr J P Wyatt, St. Louis Mo.)

The typical sequence of events occurring in a patient with carcinoma of the endometrium is described by Hertig:

> A patient has irregular bleeding preceding and following the menopause at 47 years of age. Biopsy shows cystic and perhaps adenomatous hyperplasia with anaplasia. At age 49 years bleeding continues biopsy now indicates carcinoma in situ which has developed in the preceding two years. Carcinoma in situ is present from ages 49 to 55 years, and biopsy thereafter demonstrates invasive adenocarcinoma. In other words, with a mean age incidence of 49 years for in situ cancer and 57 years for invasive cancer the mean duration of carcinoma in situ is eight years, less the average of eighteen months that endometrial cancer patients wait before consulting a physician. The net duration of carcinoma in situ of the endometrium is then estimated as six to seven years comparable to about ten years for cervical carcinoma in situ. This offers hope of good clinical results accompanying early diagnosis if conservatively made and periodically critically re-examined.

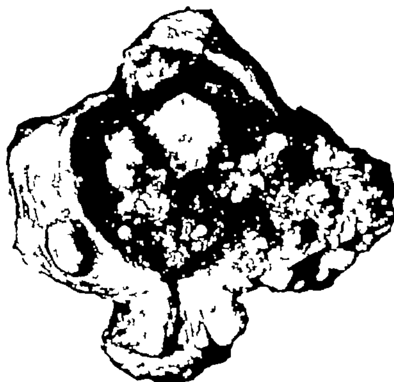


Fig 667—Extensive soft polypoid masses of carcinoma replace the entire endometrium and occur associated with leiomyomas. (EFSCH 47 2523)

Sarcoma

Endometrial sarcomas are extremely rare. They apparently arise in the supporting structure between the endometrial glands designated as lamina propria. Grossly these tumors often are a diffuse growth involving the entire endometrial surface (Fig 668). Frequently they are relatively superficial. Microscopically they have fairly uniform cells with vesicular nuclei and fine nucleoli (Fig 669).



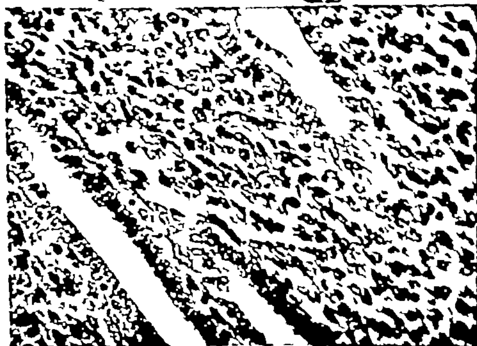


Fig. 668 —Gross photograph of an endometrial sarcoma replacing the entire endometrial cavity (EFSCH 50-658) (Courtesy Dr Richard Johnson)

Fig 669 Photomicrograph of the endometrial sarcoma shown in Fig 668. Note the uniform cells vesicular nuclei and fine nucleoli (×400) (W U neg 50-3551)

The reticulm stain is purported to be quite diagnostic because reticulin surrounds each cell (Ober) This is in contrast to the reticulin pattern of leiomyosarcoma which has wavy thick, parallel reticulm fibers that do not surround the cells. This tumor is not radiosensitive. Usually after a long time interval sarcomas of the uterus can follow irradiation (Speert)



Fig 670 —Gross photograph of a polypoid mesodermal malignant tumor of the uterus (W U neg 49-4401)

Mesodermal Mixed Tumors

Mesodermal mixed tumors of the uterus are rare (Sternberg) They occur in the uterine body or the cervix. Meikle states that those of the body are the more common. The most common site of origin is the posterior uterine wall in the region of the fundus. These tumors usually are polypoid submucosal broadly attached and often do not penetrate the deeper musculature (Fig 670) They called mesodermal because the origin is thought to be primitive mes y Liebow has grown this tumor in tissue c t growth pattern is character of normal cartilage He believes th depends upon multipo anlage rather than metaplasia. Clark tumors are of müllerian or The curettement from such a tumor e pathologist who has

seen it since the material shows proliferating immature islands of cartilage (Fig 671) In other instances the curettement reveals only undifferentiated tumor or glandular tissue thought to represent adenocarcinoma of the endometrium.



Fig 671 —Photomicrograph of an area of malignant cartilage cells in the malignant mesodermal tumor shown in Fig 670 (210) (W U neg 50 5070)

Fig 672 —Photomicrograph of striated muscle cells in a malignant mesodermal tumor (×2000) (AFIP neg 29-2563)

Multiple sections commonly show malignant change in both the stromal and epithelial elements. Malignant striated muscle cells are frequently found (Fig 672) Treatment is excision. Unfortunately in spite of the polypoid nature and superficial character the prognosis is practically hopeless.

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UTLRUS—MYOMLTRIUM

LEIOMYOMA AND LEIOMYOSARCOMA

Leiomyomas of the uterus are extremely common neoplasms about 20 per cent of all women have one or more of them. However, they are much more common in the Negro These tumors occur subserosally intramurally, or directly beneath



Fig 673 —Gross photograph of innumerable leiomyomas of the uterus. (W U neg 50-1877)

the endometrium (Figs 673-675) Uterine smooth muscle tumors (fibroids) produce symptoms referable to their size and location They may become large enough to block the ureters interfere with pregnancy or cause inflammatory com plication.

The cut surface of a typical leiomyoma has a raw silk appearance It may undergo hyaline or fatty degeneration necrosis or sarcomatous change Leio-

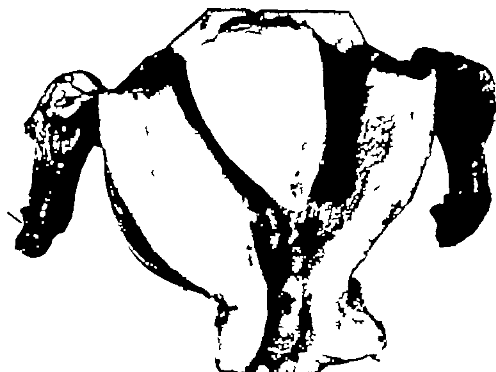




Fig 674 —Gross photograph of a single leiomyoma growing within the endometrial cavity and causing prominent signs and symptoms because of its location. (W U neg 49-4651)

Fig 675 —Gross photograph of a huge leiomyoma weighing over 1,500 grams growing mainly within the peritoneal cavity (W U neg 50-3396)

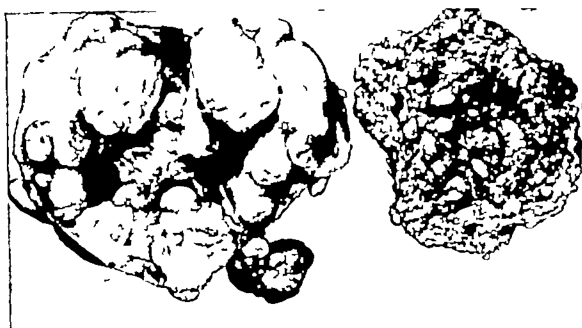


Fig 676 —Gross photograph of multiple leiomyomas and leiomyosarcoma of the uterus with multiple extremely well-differentiated metastases to the omentum. It was not possible to make the diagnosis of sarcoma microscopically (W U neg 52 3541) (Specimen contributed by Dr John Hobbs St. Louis Mo.)

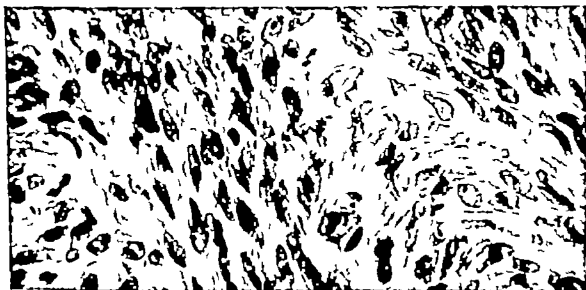


Fig 677 —Photomicrograph of a well-differentiated leiomyosarcoma of the uterus. Note resemblance to smooth muscle cells. Mitotic figures were present. This is the tumor shown in Fig. 676 and is from one of the metastases to the omentum. (×600) (W U neg 52-4483)

myomas particularly in the Negro often occur in all portions of the uterine (Fig 673) Rarely they become separated from the uterus but retain a b supply and are designated as parasitic. We have seen one attached to the ce which was mistaken for carcinoma of the cecum.

The leiomyosarcomas probably arise from pre-existing leiomyomas (Fig (Grossly malignant change should be suspected when the tumor is softer and i cellular than usual. Microscopically the tumors show an intermingling of differentiated smooth muscle cells and variable amounts of connective tissue. times wide areas become hyalinized. A leiomyoma may become infected grows into the endometrial cavity then curettement may show peculiar cells giant nuclei. With these changes an incorrect diagnosis of sarcoma often is m If leiomyomas found in uteri are routinely sectioned small zones of abno smooth muscle cells may be found. These abnormalities are common, and are indicative of sarcoma. Obvious sarcomatous degeneration of a smooth mu tumor grossly suggests a malignant neoplasm there are atypical cells, many mi figures and zones of necrosis The increase of mitotic activity is diagnosti important (Wheelock) Rarely a well-differentiated smooth muscle tumo the uterus metastasizes yet maintains its well-differentiated character (Ste (Fig 677)

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FALLOPIAN TUBES

INFECTION
PREGNANCY
CARCINOMA, PRIMARY AND METASTATIC
RARE TUMORS

INFECTION

Gonococcal infection involving fallopian tubes is common and causes luminal obliteration by progressive destruction of epithelium. Microscopically there is chronic inflammation. *Infection* of the endometrium may spread to the tube and ovary (see Ovary) Tuberculous tubal infection is hematogenous. Both tubes frequently are replaced by caseous tuberculous masses which may be mistaken for cancer both grossly and microscopically There is often extreme adenomatous proliferation of the tubal mucosa in association with the mucosal tuberculosis.

Nonspecific granulomatous inflammatory processes involving the tubes may be confusing Reaction to Lipiodol following the Ruben test may be so proliferative that it resembles neoplasm. Fibrosis incident to tuboovarian abscess may obliterate the fallopian tube. The tube enlarges its wall becomes thin, and its mucosal surface becomes smooth (hydrosalpinx) (Fig 678) The lining epithelium is compressed and cuboidal (Fig 679)

Salpingitis isthmica nodosa is usually a bilateral lesion. The tubes show a nodular surface. These nodules are white or yellowish white. There is an outpouching of the tubal mucosa and focal myohypertrophy (Fig 680) Frequently in the wall there are isolated glands surrounded by muscle However if Thorotrast is given under pressure with x ray and reconstruction, these tubal spaces are connected to the lumen of the tube (Schenken) This lesion is probably caused by inflammation and naturally often causes sterility

PREGNANCY

The development of tubal pregnancy requires previous chronic inflammation. Because of inflammatory destruction and fibrosis of lining folds the ovum is retained. Congenital abnormalities may be responsible also for retention of the ovum. The curettings from the enlarged uterus in tubal pregnancy show decidua cells without chorionic villi If these changes are associated with a tubal mass, a presumptive diagnosis of tubal pregnancy is justified and operation is indicated. With implantation of placenta in the tube the chorionic villi penetrate deeply in the wall. A tubal pregnancy terminates in several ways. Rarely rupture occurs near the end of the second month due to the destruction of the wall of the tube

myomas, particularly in the Negro often occur in all portions of the uterine wall (Fig 673) Rarely they become separated from the uterus but retain a blood supply and are designated as parasitic. We have seen one attached to the cecum which was mistaken for carcinoma of the cecum.

The leiomyosarcomas probably arise from pre-existing leiomyomas (Fig 676) Grossly malignant change should be suspected when the tumor is softer and more cellular than usual Microscopically the tumors show an intermingling of well-differentiated smooth muscle cells and variable amounts of connective tissue. At times wide areas become hyalinized. A leiomyoma may become infected if it grows into the endometrial cavity then curettement may show peculiar cells with giant nuclei With these changes an incorrect diagnosis of sarcoma often is made. If leiomyomas found in uteri are routinely sectioned small zones of abnormal smooth muscle cells may be found These abnormalities are common, and are not indicative of sarcoma. Obvious sarcomatous degeneration of a smooth muscle tumor grossly suggests a malignant neoplasm there are atypical cells, many mitotic figures and zones of necrosis The increase of mitotic activity is diagnostically important (Wheelock) Rarely a well-differentiated smooth muscle tumor of the uterus metastasizes yet maintains its well-differentiated character (Steiner) (Fig 677)

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FALLOPIAN TUBES

INFECTION

Gonococcal infection involving fallopian tubes is common and causes luminal obliteration by progressive destruction of epithelium. Microscopically there is chronic inflammation. *Infection* of the endometrium may spread to the tube and ovary (see Ovary) Tuberculous tubal infection is hematogenous. Both tubes frequently are replaced by caseous tuberculous masses which may be mistaken for cancer both grossly and microscopically There is often extreme adenomatous proliferation of the tubal mucosa in association with the mucosal tuberculosis.

Nonspecific granulomatous inflammatory processes involving the tubes may be confusing Reaction to Lipiodol following the Ruben test may be so proliferative that it resembles neoplasm. Fibrosis incident to tuboovarian abscess may obliterate the fallopian tube. The tube enlarges its wall becomes thin, and its mucosal surface becomes smooth (hydrosalpinx) (Fig 678) The lining epithelium is compressed and cuboidal (Fig 679)

Salpingitis isthmica nodosa is usually a bilateral lesion The tubes show a nodular surface. These nodules are white or yellowish white. There is an outpouching of the tubal mucosa and focal myohypertrophy (Fig 680) Frequently in the wall there are isolated glands surrounded by muscle However if Thorotrast is given under pressure, with x ray and reconstruction these tubal spaces are connected to the lumen of the tube (Schenken) This lesion is probably caused by inflammation and naturally often causes sterility

PREGNANCY

The development of tubal pregnancy requires previous chronic inflammation. Because of inflammatory destruction and fibrosis of lining folds the ovum is retained. Congenital abnormalities may be responsible also for retention of the ovum. The curettings from the enlarged uterus in tubal pregnancy show decidua cells without chorionic villi If these changes are associated with a tubal mass, a presumptive diagnosis of tubal pregnancy is justified and operation is indicated. With implantation of placenta in the tube the chorionic villi penetrate deeply in the wall. A tubal pregnancy terminates in several ways Rarely rupture occurs near the end of the second month due to the destruction of the wall of the tube

by chorionic trophoblasts. The result is severe intra abdominal hemorrhage. Abortion is the common method of termination The maternal vessels rupture into the gestation sac and cause hematosalpinx (Figs. 681 and 682) A few cases have been reported in which tubal pregnancies went to term. It is possible to conserve the ovary at operation in 80 per cent of instances.



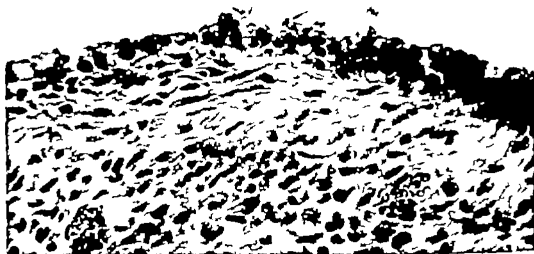


Fig. 678—Gross photograph of a large dilated fallopian tube with a smooth lining mucosal surface the end result of chronic inflammation. (W U neg 52 2469)

Fig 679—Photomicrograph of the wall of the tube illustrated in Fig 678 showing flattened lining epithelium. (×400) (W U neg 52 2475)

CARCINOMA, PRIMARY AND METASTATIC

Carcinoma may invade the fallopian tube by direct extension from the endometrium or ovary or can involve it through lymphatic channels. The primary neoplasm most commonly involving the fallopian tube secondarily is ovarian carcinoma.

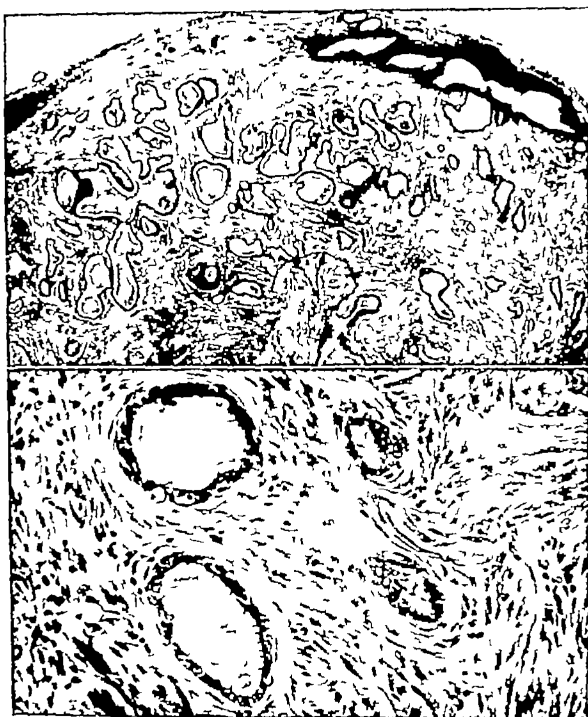


Fig 680.—Photomicrographs of salpingitis isthmica nodosa with outpouching of the tubule mucosa and prominent myohypertrophy (×250) (W U negs. 58-2715 and 58-2716)





Fig 681 —Gross photograph of hematosalpinx due to ectopic tubal pregnancy (W U neg. 52 3255)

Fig. 682 —Photomicrograph of implantation site of placenta in fallopian tube. Chorionic villus can be seen the placenta is firmly attached to the edematous wall of the tube which was filled with blood. (Low power) (W U neg 52 194)

Primary carcinoma of the fallopian tube is extremely rare. Infection is secondary and not causally related. Tubal carcinoma is rarely bilateral and the contralateral tube is normal (Finn). The criteria for the diagnosis of primary carcinoma of the fallopian tube should be highly critical. Finn's criteria are excellent:

> Grossly the tubes, at least in the distal portion, are abnormal. The dilated fimbriated end may be occluded and resemble chronic salpingitis. There is a papillary growth in the endosalpinx [Fig 683]. The uterus and ovaries are either grossly normal or are affected by a lesion other than cancer. The presence of cancer in either the uterus or the ovaries is presumptive evidence that this is the primary site, and that the carcinoma in the tube is metastatic.

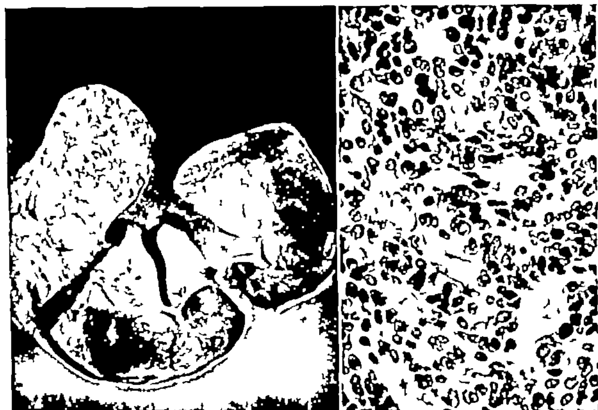


Fig 683 —Gross photograph of carcinoma of the fallopian tube with extensive replacement of the tube. The uterus and ovaries were normal (W U negs. 50-1683 and 50-1684.)

Fig 684 —Photomicrograph of tumor shown in Fig 683. It is a poorly differentiated adenocarcinoma. (×400.) (W U neg 52 3600.)

> Microscopically the epithelium of the endosalpinx is replaced in whole or part by adenocarcinoma [Fig 684]. The histological character of the cells resembles the epithelium of the endosalpinx. The endometrium and ovaries are normal, affected by a benign lesion, or contain a malignant lesion that by its small size, distribution and histological characteristics appears to be metastatic from the tube. The prime involvement is in the endosalpinx; the perisalpinx and the lymphatics of the muscularis and the mesosalpinx are rarely involved. Tuberculosis has been carefully excluded.

RARE TUMORS

Mesothelioma, a rare benign tumor arises from the peritoneum and involves the surface of the fallopian tube it is mentioned only because it may be mistaken for malignant neoplasm (Evans) This lesion has been described in the section on *Epididymis and Spermatic Cord (Male Reproductive System see p 598)* Other rare tumors include dermoid cyst (Aaron), leiomyoma, and sarcoma.

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OVARY

INTRODUCTION

Ovarian diseases of surgical importance can be broadly divided into non neoplastic cysts and neoplasms. Except for endometriosis and inflammation, pathologic processes are infrequent. Nonneoplastic cysts are unfortunately too commonly seen as surgical specimens. It has been said that if the ovaries were placed externally their removal would be undertaken with more hesitation The general surgeon exploring the abdomen may find a mildly cystic normal ovary and unfortunately remove it. The risk of carcinoma developing is much less than has been assumed. The common assumption that ovarian substitutes will do almost everything for a woman except have her baby is false (Miller)

NONNEOPLASTIC CYSTS

Nonneoplastic cysts of the ovary develop by cystic distention of follicles, luteinized corpora atretica (lutein cysts) or corpora lutea. The epithelium within these cysts tends to be flattened. If the epithelial lining disappears they collapse.

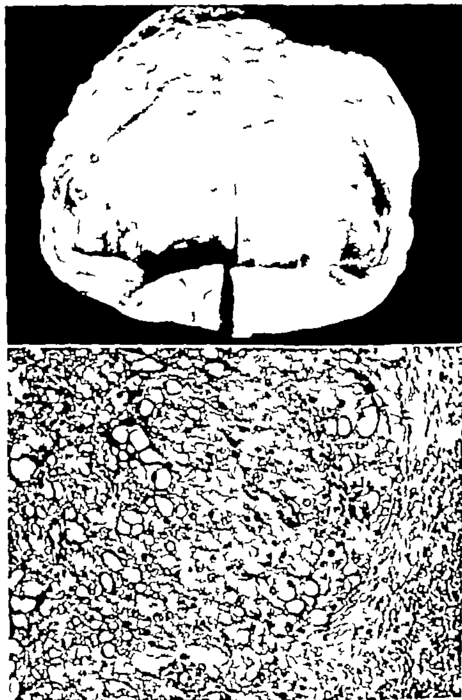


Fig 685 —Gross photograph of corpus luteum cyst. This cyst was found at the time of exploration for another condition, and the surgeon incorrectly removed it. (W U neg. 52 1978)

Fig 686 —Photomicrograph of the wall of the cyst shown in Fig 685 composed of luteinized granulosa. (×170) (W U neg 52 2041)

The *follicular cysts* may be single or multiple Their lining consists of compressed granulosa cells next to a thin layer of theca cells The fluid within follicular cysts may contain estrogenic hormone Follicular cysts usually do not get larger than 10 cm Smaller follicular cysts 5 to 15 mm in diameter are usually bilateral and represent immature follicles which have become cystic because of inflammation or hormonal stimulation The *corpus luteum cysts* are single and usually less than 6 cm in diameter, they may develop at the end of the menstrual cycle or occur in pregnancy (Figs. 685 and 686) The wall is composed of a luteinized granulosa The fluid content often is bloody When hemorrhage into the cystic cavity ruptures into the peritoneal cavity an erroneous diagnosis of ruptured ectopic pregnancy may be made.

Follicular and Corpus Luteum Cysts

Approximately 50 per cent of all ovarian tumors are 5 cm. or less in diameter In Miller's series 97 per cent were simple cysts of the graafian follicle and corpus luteum. Of 461 small ovarian cysts only 3 per cent were neoplastic and only 3 cases were malignant The symptoms associated with small cysts disappeared without excision in over 80 per cent of the patients. Carpenter analyzed 1 137 separate gynecologic specimens 314 were ovarian. Table 27 indicates the high percentage which were nonneoplastic.

Table 27 Three Hundred Fourteen Ovarian Specimens*

		Per cent	
Follicle	179	57 0	~78 9 (Follicle, Simple, Corpus luteum)
Simple	36	11 1	
Corpus luteum	33	10 8	
Chronic oophoritis	32	10.3	
Hemorrhagic cyst	16	5 1	
Pseudomucinous	6	1 9	
Serous cystadenoma	3	1 0	
Carcinoma	2	0 6	
Krukenberg	2	0 6	
Fibroma	2	0 6	
Dermoid	2	0 6	
Granulosa-cell tumor	1	0.3	

*From Carpenter C. C. Tr M Soc., North Carolina pp 236-242 1936

The graafian follicle ruptures in the midmenstrual period when the ovum reaches the surface. Thus is physiologic the amount of intraperitoneal bleeding which occurs is rarely severe. The follicle soon seals and the yellow luteal cells of corpus luteum develop The corpus luteum persists only if the woman becomes pregnant. If the corpus luteum ruptures (one or two days premenstrually) the bleeding may be severe (500 c.c. or more) (Hoyt) The small elevated bluish nodules of *endometriosis* may occur in one or both ovaries on the peritoneum adjacent to the ovary or in the cul-de-sac. These nodules may be present on the surface of the involved ovary or be seen on cross section. Hemorrhage in such an ovary often forms a cystic mass (chocolate cyst) (Fig 687) Ectopic decidual reaction in the absence of current or recent pregnancy can occur In 14 of 16 cases reported by Ober a functioning corpus luteum which had undergone destruction was present.

FROZEN SECTION

When patients undergo operation for ovarian tumor the pathologist should be present. He can be of help in the gross diagnosis and can use frozen section as indicated. The decisions involve these questions. Should only the involved ovary or ovaries be removed? Should a hysterectomy be performed? Most



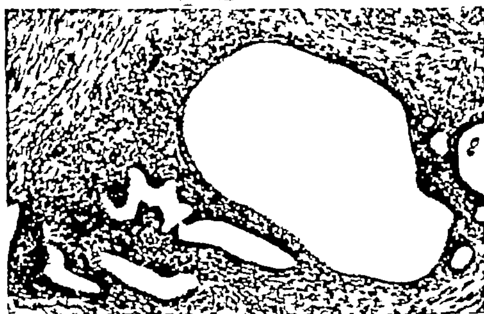


Fig 687.—Gross photograph of chocolate cyst of the ovary due to endometriosis. There were also endometrial implants on the endometrial surface. (W U neg 52 3852.) (Specimen contributed by Dr Willard Allen, St. Louis Mo.)

Fig 688.—Photomicrograph of endometriosis with glands and typical stroma. (×150) (W U neg 50-3945)

ovarian tumors are relatively simple to recognize—at least it can be decided whether they are benign or malignant The age of the patient influences the extent of the operation if the lesion is benign but if the tumor is malignant age must not be allowed to limit its adequate removal The pathologist and surgeon should remember

1 *Remove only the involved ovary in benign tumors* Normal ovarian tissue of this ovary at times can be preserved These tumors include fibroma, thecoma, Brenner tumor, and teratoma (dermoid type)

2 Certain malignant neoplasms tend to be unilateral These tumors include pseudomucinous cystadenocarcinoma (about 15 per cent bilateral), dysgerminoma (rarely bilateral) granulosa cell tumor, and arrhenoblastoma Occasionally ovariectomy alone may be adequate In other instances hysterectomy and bilateral salpingoovariectomy are required because of the size of the neoplasm and the possibility of its extension

3 Certain malignant tumors tend to be bilateral. These include serous cystadenocarcinoma (about 40 per cent) carcinoma and unclassified tumors (high percentage)

INFLAMMATION

Nonspecific inflammation of the ovary occurs as a complication of infection from the endometrium forming a tubal ovarian abscess. Specific infections such as tuberculosis occur in the ovary invariably this is hematogenous in origin and often also involves the endometrium In time the infection may subside and leave a large tubal ovarian cystic mass.

ENDOMETRIOSIS

Endometriosis of the ovary is common and may or may not be associated with adenomyosis of the uterus. The pathogenesis of some instances of endometriosis of the ovary probably is related to transplantation of endometrium from the endometrial cavity (Javert) Coelomic metaplasia is also an important mechanism of origin of primary pelvic endometriosis (Hertig) Endometriosis usually occurs in childless women The process often is active for many years. At operation small blueberry like spots may be seen on the surface of the peritoneum. These blue areas are slightly raised and surrounded by fibrosis (Fallon) The entire ovary itself may be converted to a chocolate cyst as a result of repeated hemorrhage within it (Fig 687) Infrequently such cysts perforate. The ovary involved by endometriosis often is fixed by fibrous adhesions. Microscopically typical endometriosis may be seen although in chocolate cysts multiple sections are frequently necessary to prove the diagnosis (Fig 688) The more advanced the endometrial lesion the more difficult the diagnosis. To be absolutely certain the pathologist should find endometrial epithelium, glands stroma, and hemorrhage. The endometrial stroma is responsible for the bleeding and may have typical "naked nucleus" cells surrounded by reticulin and a typical spiral arteriole in conjunction with old and recent hemorrhage. Unfortunately this combination of findings is rarely present.

TUMORS

Embryology

The classification of ovarian tumors is based on embryology The sex gland anlage is an accumulation of cells beneath the coelomic epithelium on the anterior ventral surface of the wolffian body In this indifferent phase it is impossible to determine histologically whether the sex gland is ovary or testis. The cells which become disassociated from germinal function may in later life give rise to the tumor designated as dysgerminoma. These tumors naturally have no endocrine function. In the testes they are known as seminoma. At the beginning of sex differentiation sex cords or medullary tubules develop and converge in a zigzag fashion toward the hilum of the gland.

When a gonad becomes an ovary, there is preliminary sex cord differentiation which soon regresses further ovarian differentiation proceeds about the remains of this early testicular scaffold Certain potentially male cells of the preliminary testicular phase may persist in the medulla of the ovary and be the cells from which arrhenoblastomas arise. Cell rests of developing ovarian mesenchyma probably are the source of thecomas and granulosa cell tumors. Gillman believes in individual origin in granulosa and theca cells, and emphasizes that their mingling in neoplasms is related to the fact that there is one stage in embryologic development when they are closely associated.

Serous Cystadenoma, Mucinous Cystadenoma (Pseudomucinous)

The serous cystadenomas make up almost one third of all ovarian tumors. Their pathologic evaluation is extremely important in prognosis. A high percentage of them are bilateral (30 to 50 per cent) Grossly they form rather large masses which usually contain serous fluid rarely the fluid is viscous. In the better differentiated tumors papillary projections may extend through the wall and onto the surrounding peritoneal surfaces (Fig 689) The more malignant tumors commonly are solid show areas of necrosis, and invade through the wall of the ovary

Mucinous cystadenoma of the ovary has been until recently designated as pseudomucinous The epithelium and cyst contents contain for the most part acid mucopolysaccharides. Mucins are chemically characterized as mucopolysaccharides therefore the term pseudomucinous is incorrect (Hertig Canker) Mucinous cystadenoma of the ovary is about as frequent as serous cystadenoma, but it is not as often bilateral (5 to 15 per cent) Hertig believes that the germinal epithelium of the ovary is potential mullerian epithelium. From the müllerian system is formed tubal mucosa, endometrium endocervix, and a portion of vagina. He feels that mucinous tumors of the ovary resemble cervical epithelium, and that the serous type of cystadenoma resembles fallopian tube epithelium. It is probable that some mucinous cystadenomas arise from a teratoma. They often have obvious intestinal mucosa and may contain intestinal enzymes (lipase, trypsin, amylase, and sucrase) (Canker) The mucinous tumor contains a viscid fluid and tends to grow larger than the serous type (Fig 690) It may have papillary

Fig 689 —Gross photograph of well-differentiated serous cystadenoma of the ovary with papillary projections. (W U neg 50-1682.)

Fig 690 —Gross photograph of a large mucinous cystadenoma of the ovary (W U neg 52-4101) (Courtesy Dr A. O Severance San Antonio Texas.)



Fig 691 —Photomicrograph of a well-differentiated benign fibrous serous cystadenoma. (×200) (W U neg 50-3848.)

Fig 692 —Photomicrograph of a well-differentiated serous cystadenoma with "psammoma" bodies (×110) (W U neg 48-4714)

projections and, if malignant, develops solid areas which invade the remainder of the ovary

Whether or not serous cystadenoma is benign or malignant greatly influences the end results (Taylor) The five year survival rate will be greater if the pathologist is not conservative. There is little doubt that the benign tumors are predominantly fibrous with a single layer of lining cells and are without invasive tendencies (Fig 691) In the well-differentiated neoplasms calcific spherules called psammoma bodies may be present (Fig 692) The moderately well-differentiated



Fig. 693 — Photomicrograph of an obviously malignant serous cystadenocarcinoma of the ovary (×200) (W U neg. 50-3847)

Fig 694 — Photomicrograph of serous cystadenoma of questionable malignancy (×200) (W U neg 50-3846.)

tumor can show areas of squamous change and be designated as an adenoacanthoma (Garnet) However even in the apparently microscopically benign variant there have been occasional instances of metastases In a group of 13 such cases reported by Marchetti, there was one death. There is little doubt as to the malignancy of the cellular tumor which shows layering of cells prominent variation in the size and shape numerous mitotic figures, and invasion of the stalk (Fig 693) It is the interpretation of the borderline group of tumors that is most difficult (Fig 694) The tumor showing more complex branching with beginning

layering of lining cells has an increased tendency to invade (Brakemann) These tumors tend to implant upon the peritoneal surface, but they also metastasize to regional lymph nodes, liver and more distant organs. A variant of this tumor is the cystadenofibroma which is made up of small cysts and fibroma like stroma. This cortical stroma is not ordinarily fibrous tissue but has minimum amounts of fat and is related to the theca externa of the follicle. The most benign appearing of this variant can at times metastasize (Hertig)

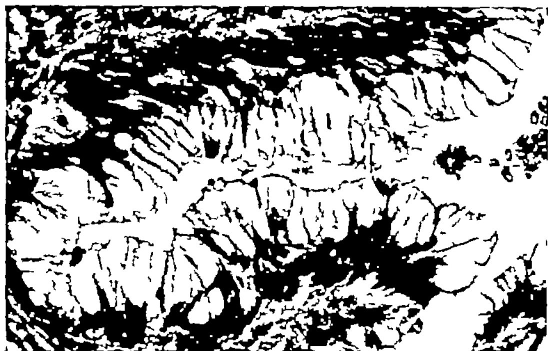


Fig 695 —Photomicrograph of a well-differentiated pseudomucinous tumor The individual cells are tall columnar with basally situated nuclei. (×400) (W U neg 50-476)

The benign variant of mucinous cystadenoma is lined by tall columnar nonciliated cells with basally situated nuclei (Fig 695) Goblet cells and argentaffin cells may be present (Reagan Masson) Evidences of malignancy are increased layering of cells, anaplasia, and invasion of the stalk in the areas of papillary branching This tumor tends to implant upon and locally invade surrounding tissues such as the bowel the abdominal wall and bladder At times gelatinous masses of tumor within the distended abdomen cause intestinal obstruction and peritonitis frequently supervenes. Metastases to distant areas are infrequent. Table 28 summarizes the important differences between these two tumors.

Teratoma

Most teratomas of the ovary are benign in Allan's series, 313 were benign and 3 malignant (1 per cent) (Table 29) However teratomas made up almost 20 per cent of the entire group of ovarian neoplasms. Grossly these tumors are usually unilateral (12 per cent bilateral) and provoke only symptoms relating to mass. The greasy material within them is liquid at body temperature. If a teratoma ruptures into the peritoneal cavity the greasy fluid provokes a prominent fibroblastic

TABLE 28 DIFFERENTIAL CHARACTERISTICS OF SEROUS AND MUCINOUS TUMORS OF OVARY

	SEROUS	MUCINOUS
Frequency	Benign varieties about equal in frequency malignant types predominantly serous	
Bilateral	50 per cent	5 per cent
Size	Moderate	Often huge
Character of fluid	Transudate	Slimy viscid
Malignant	High percentage	Low percentage
Tendency to metastasize to regional and distant lymph nodes in malignant type	High percentage	Low percentage
Tendency to implant	High percentage	Moderately frequent
Microscopic characteristics	Cuboidal	High columnar basally situated nucleus
Cilia	Often present	Never present
Psammoma bodies	Frequent in well-differentiated types	Never present

TABLE 29 INCIDENCE OF OVARIAN TUMORS*

MICROSCOPIC TYPE	BENIGN TUMORS NUMBER	BENIGN TUMORS PER CENT OF TYPE	MALIGNANT TUMORS NUMBER	MALIGNANT TUMORS PER CENT OF TYPE	BENIGN AND MALIGNANT TUMORS NUMBER	BENIGN AND MALIGNANT TUMORS PER CENT OF ALL TYPES
Serous	347	68 4	160	31 6	507	29 1
Pseudomucinous	361	87 0	54	13 0	415	23.8
Unclassified cystadenoma	36	100 0			36	2 1
Dermoid cyst	313	99 0	3	1 0	316	18.2
Granulosa-cell	26	70.3	11	29 7	37	2 1
Fibromas	359	100 0			359	20 6
Brenner	20	100 0			20	1 1
Miscellaneous benign†	13	100 0			13	0 7
Undifferentiated carcinoma			24	100 0	24	1 4
Hypernephroma (Grawitz)			6	100 0	6	0.3
Endometriocarcinoma			3	100 0	3	0.2
Dysgerminoma			2	100 0	2	0 1
Carcinosarcoma			2	100 0	2	0 1
	1 475	84 8	265	15 2	1 740	100 0

*From Allan M S., and Hertig A F Am. J Obst. & Gynec. 58 640-653 1949
†Including leiomyoma arrhenoblastoma adenomyoma and paraganglioma.

peritonitis resulting in nodules simulating exactly metastatic cancer The diagnosis is resolved by frozen section (Auer) Usually they are multiloculated and contain a well-defined nipplelike structure covered with hair they often contain teeth or an imperfectly formed mandible other well-organized structures are rare (Fig 696) Microscopically they are lined by well-differentiated stratified squamous epithelium Skin appendages are extremely common brain and nerve tissue occur frequently and thyroid tissue is found in about 10 per cent of them The number of different tissues found depends on the number of sections studied the most rewarding sections are those from the nipplelike structure even if it contains bone In a thorough study of 225 teratomas by Blackwell ectodermal derivatives were present in 100 per cent mesodermal structures in 93 per cent, and entodermal derivatives in 71 per cent. The malignant teratoma is usually squamous carcinoma. Numerous other reported types of tumors include primary choriocarcinoma of the

ovary (*Marrubini*) and carcinoid tumors (*Stewart*) we have seen sweat gland carcinoma.

Thyroid tissue is probably the most interesting tissue occurring in cystic teratoma of the ovary (struma ovarii) (Fig 697) This entity represents dominant growth of a single tissue in a teratoma, about 150 cases have been reported.



Fig 696 —Gross photograph of benign teratoma (dermoid cyst) of the ovary showing greasy contents and hair (W U neg 50-1876)

Fig 697 —Gross photograph of a teratoma of the ovary demonstrating the typical gross appearance of struma ovarii. This tumor was composed almost entirely of thyroid tissue (EFSCH 51 2608. Contributed by Dr Richard Johnson.)

This thyroid tissue may show all pathologic changes seen in a normally placed thyroid including nodular goiter, hyperplasia and true thyroid neoplasms (Emge) There is no doubt that this tissue is true thyroid tissue a concept further substantiated by biologic tests (Plaut)

Granulosa Cell Tumors and Thecomas

Granulosa cell tumors account for approximately 10 per cent of all solid ovarian tumors About 10 per cent are bilateral, they are often cystic and hemorrhagic, and vary in size from microscopic masses to tumors filling the abdomen (Fig 698) We have seen one granulosa cell tumor in a 60 year-old woman who had endometrial hyperplasia without palpable tumor Both ovaries appeared normal but in one there was a microscopic granulosa cell tumor These tumors are encapsulated and have a smooth lobulated surface The cysts contain straw colored or mucoid fluid. The solid portions of tumor frequently are gray but may show focal yellow areas caused by luteinization of the tumor Three of Hodgson s 62 cases showed luteinization



Fig. 698.—Gross photograph of a large cystic and hemorrhagic granulosa cell tumor of the ovary (EFSCH 48 28.)

The microscopic pattern of the granulosa cell tumor is extremely variable different parts of the same tumor may show dissimilar patterns The folliculoid type of cell arrangement is the most common it suggests a normal follicle of the ovary (Figs 699 and 700) The tumor may have a cylindroid pattern with cystic phases, and rarely may have a sarcomatoid or even adenomatoid appearance (Traut Varangot) A single granulosa cell tumor may show the typical granulosa cell pattern blending with the typical pattern of a thecoma.

In about 65 per cent of instances the *thecoma* appears after menopause (McGoldrick) and is invariably unilateral benign, and rarely cystic. It varies considerably in size, has a well-defined capsule and cuts with increased resistance. The tumor resembles a fibroma (Fig 701) However the small yellow areas in thecomas are the most helpful positive finding in differentiating these tumors from fibromas. Microscopically these yellow areas contain clumps of spindle cells with

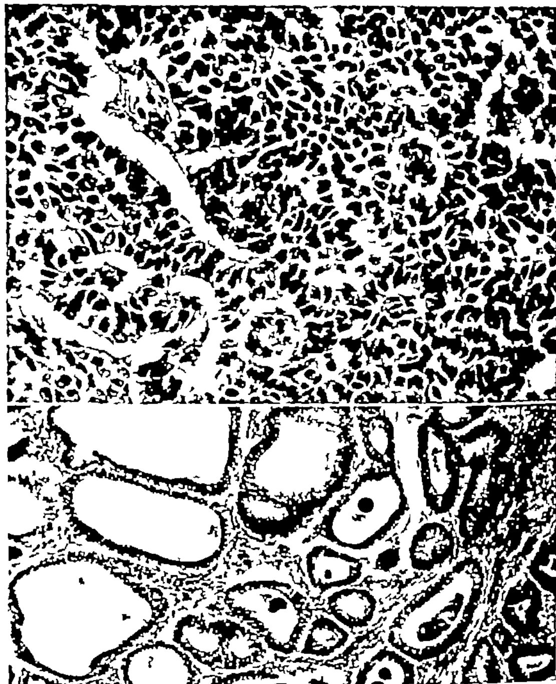


Fig 699 —Photomicrograph of a typical granulosa cell tumor of the ovary with a folliculoid pattern. (×400) (W U neg 50-3555)

Fig 700 —Photomicrograph of prominent endometrial hyperplasia occurring in association with the tumor shown in Fig 699 (×115) (W U neg 50-3556)

centrally placed nuclei and lipid rich cytoplasm (Fig 702) The intervening tissue may show considerable hyalinization and contain focal hyaline plaques. The epithelial cells in this connective tissue network may have vacuolated or acidophilic cytoplasm and clearly defined polyhedral cell boundaries giving the cells a lutein like appearance (Henderson)

Thecomas of the ovary may have prominent stromal hyperplasia this is uncommon in patients under 40 and is of greatest frequency in the sixth decade

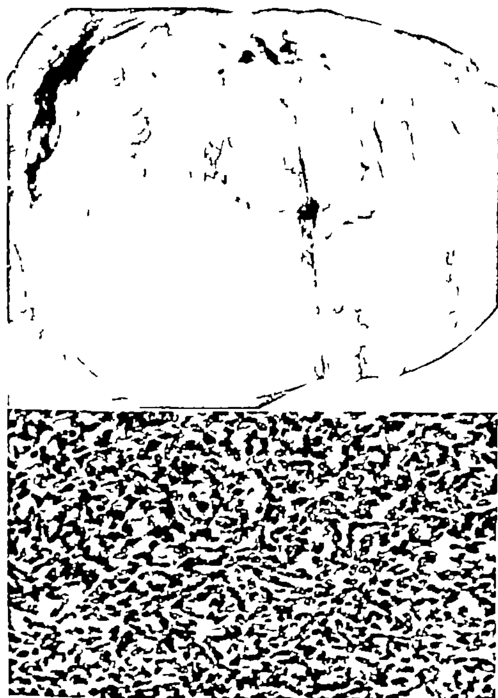


Fig 701 – Gross photograph of large thecoma which has small yellow areas. (W U neg 49 5296)

Fig 702 – Photomicrograph of a typical highly cellular thecoma with spindle cells and hyaline-like plaques (×400) (W U neg 52 34_0)

(Sternberg) These findings suggested to Sternberg that stromal hyperplasia is the soil in which theca cell tumors are likely to develop He feels that transition can be traced from stromal hyperplasia through diffuse thecomatosis to theca cell tumors.

Granulosa cells are reticulin free and theca cells are individually surrounded by reticulin. However in a theca cell tumor there are invariably islands of reticulin free cells. Luteinized cells when found in a thecoma are almost invariably reticulin free (Henderson)

Effects of Hyperestrogenism in Granulosa and Theca Cell Tumors.—Both of these tumors may produce clinical signs of hyperestrogenism particularly in prepubertal and postmenopausal patients. *Precocious puberty occurs in the former* prominent menstrual abnormalities in the latter These tumors frequently produce enlargement of the uterus characterized by muscle hypertrophy and prominent endometrial hyperplasia. However not all thecomas and granulosa cell tumors function we have seen cases with atrophic endometrium. Histochemically Dempsey and McKay found that the graafian follicles of both the rat and human ovaries have steroid substances confined to the thecal layer None were present in the granulosa layer *McKay demonstrated that histochemical studies helped differentiate* thecomas from fibromas and demonstrated the functional state of the tumor Estrogens come from thecal cells of the thecoma and from thecalike cells in granulosa cell tumors. In the granulosa cell tumors it is the thecal component rather than the tumor cells which produce hormone. Histochemical agents cannot differentiate inactive thecoma from fibroma.

Occurrence of Carcinoma of the Endometrium With Granulosa Cell Tumors and Thecomas.—Functioning granulosa cell tumors and thecomas cause endometrial hyperplasia with such extreme atypical changes that a mistaken diagnosis of carcinoma is often made. The fact that complete regression of these changes *occurs after simple removal of the functioning ovarian tumor is evidence* that the atypical changes are not truly cancer Stohr reported a case diagnosed as endometrial adenocarcinoma before removal of a granulosa cell tumor A repeat curetting of the endometrium five weeks postoperatively showed normal early typical secretory epithelium coinciding with the clinical phase of the menstrual cycle

Henderson reported two endometrial carcinomas among 21 cases of granulosa *cell tumors and 3 others among 9 patients with thecomas*

In all instances the endometrium was diffusely involved but the myometrium was only superficially invaded. Glandular epithelium was of the secretory type. It is interesting that none of these patients suffered recurrence or died from cancer Banner reported 55 postmenopausal thecomas and granulosa cell tumors with associated uterine carcinoma in 27 3 per cent. In 82 granulosa cell tumors and 16 thecomas reported by Kottmeier there were 4 carcinomas of the endometrium. In 9 of the same group the endometrium showed atypical changes which were not considered carcinoma but could easily have been confused with it. Novak reported atypical endometrial hyperplasia simulating adenocarcinoma in patients *who received estrogens.* It seems apparent that carcinoma of the endometrium

has been often incorrectly diagnosed in the presence of theecoma and granulosa cell tumors

We have seen several estrogen producing Sertoli cell tumors of the ovary Homologous tumors occur both in the human and canine testes (Teilum Scully)

In a paper by Teilum he states his viewpoint as follows

> According to this view the male directed cells derived from a common gonadal blastema comprise estrogen producing Sertoli cells and androgen producing Leydig cells. Thus androblastoma may exhibit no endocrine effect on the host whether male or female or they may be feminizing or virilizing depending on the types of effective functioning cells In support of this statement, it should be noted that arrhenoblastomas with androgenic activity contain a considerable component of stromal cells analogous to Leydig cells, while the testicular and ovarian androblastoma associated with feminization were in great part composed of tubular structures with lipid laden cells

He reserves the term arrhenoblastoma for certain ovarian tumors which produce masculinizing effects because of androgen producing Leydig cells. Therefore this term will not characterize the feminizing ovarian Sertoli cell tumors Teilum has also observed a granulosa cell tumor in the testis

Dysgerminoma

There have been about 400 cases of dysgerminoma reported in the literature (Mueller) This tumor is common in prepubertal children and in adolescents (Novak) Santesson collected 299 cases 81 per cent of the patients were under 30 and 44 per cent were under 20 years of age This tumor is often large (over 1 000 grams) and occurs most frequently in the right side. Approximately 15 per cent are bilateral (Santesson) It has a smooth often convoluted surface which may resemble cerebral cortex (Potter) (Fig 703) There is frequently a well-defined fibrous capsule The cut surface is gray cellular and frequently has yellow and brown areas of hemorrhage and necrosis. Unlike the granulosa cell tumors cysts are infrequent. Microscopically the histogenesis of this tumor has been debated The majority opinion holds that it arises from indifferent sex cells at the hilum of the ovary In the earliest stages of the development of the ovary the anlage of the gonad is a collection of cells on the ventral surface of the wolffian body The cells from which this tumor arises are neuter possessing neither male nor female attributes hence dysgerminal This tumor in the past was called large-cell carcinoma. The tumor cells may have a semitubular or cordlike arrangement individual cells are uniform have large nuclei one or two nucleoli and poorly defined cytoplasmic outlines (Fig 704) Glycogen and sometimes fine droplets of fat are present in the cytoplasm. The stromal contents vary there may be hyaline change in vessels lymphocytic infiltration focal necrosis and areas of pseudotubercle formation Dysgerminoma has exactly the same origin microscopic pattern, and clinical behavior as does seminoma of the testes Reifferscheid has reported focal folliculoid changes of granulosa like epithelium in one case. The microscopic pattern is of no value in prognosis (Seegar) Scully described in dysgerminoma the focal presence of cells of sex-cord and mesenchyme origin and designated these ovarian tumors as "gonadoblastomas

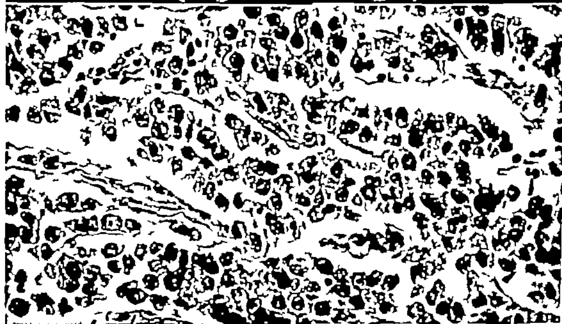


Fig 703 —Gross photograph of a large dysgerminoma with an external surface suggesting convolutions of the cerebral cortex. (From Potter E. B Am. J Path. 22: 551 1946.)

Fig. 704 —Photomicrograph of a typical dysgerminoma with a semitubular or cordlike arrangement. Individual cells are uniform with large nuclei and prominent nucleoli (×340) (W U neg 50-3761)

Clinicopathologic Correlation.—Dysgerminoma is the tumor most common in females with pseudohermaphrodism similarly seminoma is the tumor most common in males with cryptorchidism However, over one half of dysgerminomas occur in normal women Hypoplasia of genitals and hirsutism may occur Removal of these tumors has no effect on these sex changes (Novak) Patients with small tumors or tumors confined to the ovary have the best prognosis. If the tumor extends outside the capsule or is bilateral prognosis is less favorable (Santesson) These malignant tumors are radiosensitive (Moreton) Infrequently the Friedman test is positive

Masculinizing Tumors—Arrhenoblastoma

In the ovary lesions which may cause masculinization include *hyperplasia of human ovarian hilar cells* (extraglandular Leydig cells), *true tumors of such cells tumors arising from adrenal heterotopic cortical rests and arrhenoblastomas*

Arrhenoblastomas are rare particularly after the menopause. About 140 acceptable cases have been reported (Hughesdon) Grossly arrhenoblastoma is almost invariably unilateral with a well-defined connective tissue wall. Normal ovarian tissue often is seen on section the tumor may show multicentric nodularity cyst formation and areas of hemorrhage (Fig 705) It is often very cellular and gray in appearance A high proportion of the tumors have low malignant potential This tumor apparently arises from male gonadogenic cells in one or another phase of development this causes the histologic picture to vary (Meyer) There is general agreement that the primitive female follicular apparatus is differentiated only after a preliminary and aborted male sex scaffolding has been laid down (Novak) Meyer's concept that male-directed cells remain latent in the ovary especially in the region of the rete ovarii is a logical one it is from these cells that arrhenoblastomas arise. The well-differentiated type is called an "adenoma tubulare testicularis of Pick and resembles closely seminiferous tubules (Fig 706) With such a tumor secondary sex alterations may be entirely absent. The more undifferentiated tumors appear sarcomatous Hertig states "The arrhenoblastoma mimics the embryonic testis in a broad morphologic spectrum and generally masculinizes in proportion to the amount and differentiation of the hormone producing interstitial stroma." Some tumors are admixtures of well differentiated and poorly differentiated areas

Clinicopathologic Correlation.—Arrhenoblastoma of the ovary frequently occurs in women 20 to 30 years of age (Novak) The tumor is relatively rare after menopause. Clinically defeminization occurs manifested by amenorrhea atrophy of the breasts and loss of subcutaneous fatty deposits there is also hypertrophy of the clitoris and deepening of the voice (masculinization) Usually prompt return of feminine characteristics follow excision of the tumor but the positive manifestations of masculinization disappear more slowly

Masculinizing Tumors Arising From Heterotopic Adrenal Rests

Adrenal cortical rests are rare in the ovary (Nelson) They usually are found in the broad ligament are circumscribed, encapsulated bright yellow and measure

1 to 3 mm. in diameter Microscopically such rests often show good adrenal cortical zone orientation These rests are much more common in children but are found in adults Masculinizing tumors arise rarely from heterotopic adrenal

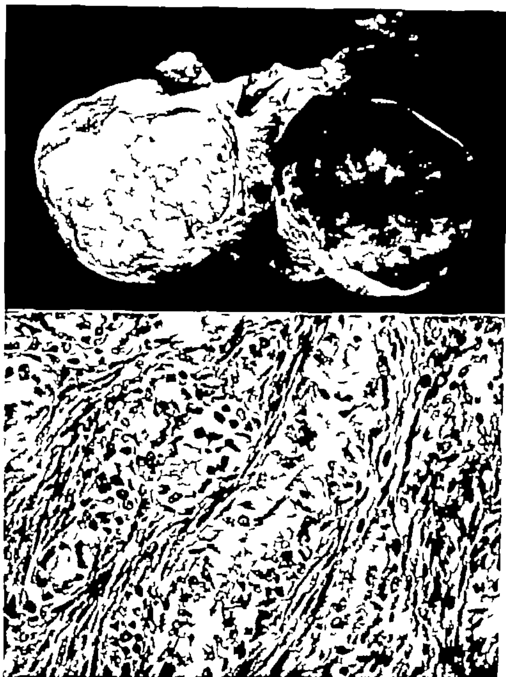


Fig 705.—Gross photograph of an arrhenoblastoma with multicentric nodulation. (From Dockerty M B. Proc. Staff Meet. Mayo Clin. 14: 369-374 1939)

Fig 706.—Photomicrograph of a well-differentiated arrhenoblastoma in which the pattern closely resembles seminiferous tubules. (×400) (W U neg 50-6474)

cortical tissue in or near the ovary (Kepler) Such tumors are usually benign, but we have seen a malignant one. *It is less reasonable to believe that these tumors* arise from luteinized granulosa cells the corpus luteum is a transient structure,

granulosa cell tumors often become partially luteinized, both the granulosa and theca cell tumors are feminizing and cannot logically be associated with virilism (Schiller) A tumor in the region of the ovary causing Cushing's syndrome (stria hypertension osteoporosis and diabetes) could not originate in the corpus luteum. A masculinizing tumor in the region of the ovary having a high content of de hydroisoandrosterone (Allen Patterson) must have arisen from adrenal cortical tissue. Probably most adrenal rest tumors or luteomas represent virilizing neoplasms with an overgrowth of Leydig cells (Teilum)

Hyperplasia and Tumors of Ovarian Hilar Cells (Extraglandular Leydig Cells)

The hili of 80 per cent of adult human ovaries contain nests of cells morphologically identical to testicular Leydig cells (Sternberg) Individual cells measure 14 to 25 microns in diameter and have a vesicular nucleus with acidophilic granular cytoplasm The cytoplasm contains lipids which stain with sudan III a small amount of gold brown lipochrome pigment and may contain acidophilic rodlike structures known as the crystalloids of Reinke These extraglandular Leydig cells have been called sympathicotropic cells by Berger because of their intimate association with nerves. Hyperplasia or neoplasia of these cells may produce masculinization, they probably normally produce androgen. Such lesions are extremely rare however Sternberg reported four instances of masculinization in which two were due to hyperplasia and two to benign neoplasms of extraglandular Leydig cells. Furthermore hyperplasia of these hilar cells is found following the administration of chorionic gonadotropin in pregnancy and in the presence of choriocarcinoma Such occurrences are further evidence relating these cells to the Leydig cells of the testis (Sternberg 1953)

Brenner Tumors

About 175 Brenner tumors have been reported nearly 75 per cent occur in patients over 40 years old (Gaines) Grossly these benign tumors vary greatly in size and are almost always unilateral. Invariably they are firm, white or yellowish white, and may contain small cystic areas filled with opaque viscous yellow brown fluid. Rarely a solid Brenner tumor occurs in the wall of a mucinous or less frequently in a serous cystadenoma. Microscopically Meyer believes that the coelomic epithelium within the ovarian cortex gives rise to small groups of cells designated as Walthard cell nests. Walthard found that the sexually indifferent cell complexes in ovaries of newborn babies and infants were at times accompanied by epithelial cysts This same type of epithelial formation has been found beneath the serosa of the tubes and mesosalpinx solid Brenner tumors theoretically might originate in them (Muller) However tumors from this area have not as yet been reported. Muller found these rests within the ovarian parenchyma in 2.8 per cent of 251 operative specimens Brenner tumors consist of nests of closely packed cells with clear cytoplasm, deeply staining nuclei and distinct nucleoli which are surrounded by finely fibrillated connective tissue (Fig 707) Cystic degeneration occasionally produces cavities lined by flattened, cuboidal, or cylindrical cells in the centers of these epithelial areas The cells may secrete mucin

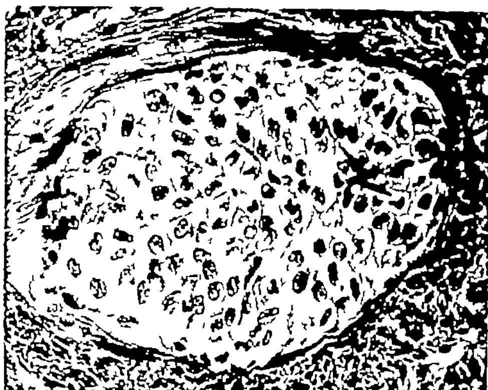


Fig 707 —Photomicrograph of characteristic collection of closely packed cells with clear cytoplasm and deeply staining nuclei seen in a Brenner tumor (High power) (W U neg 49-6946.)



Fig 708 —Photomicrograph of mucinous tumor and a Brenner tumor The mucinous tumor with a typical lining epithelium is to the right, and the Brenner tumor with its characteristic collection of cells is to the left. (W U neg 50-6473) (Slide contributed by Dr Richard Johnson, Ellis Fischel State Cancer Hospital, Columbia, Mo.)

rarely this tumor is associated with mucinous cystadenoma (Fig 708) This tumor at times is confused with a granulosa cell tumor containing lipoid material Lipid is entirely absent in the Brenner tumor In addition Brenner tumors contain glycogen while granulosa cell tumors do not (Fox) In order to diagnose Brenner tumor the fibromatous connective groundwork surrounding characteristic epithelial masses must be present (Novak)

Clinicopathologic Correlation —A high proportion of Brenner tumors occur in patients over 50 years of age They do not cause endocrine abnormalities The growth rate is slow and ascites is rare

Fibroma

Fibromas of the ovary are common and occur almost invariably after puberty They are solid lobulated encapsulated firm and usually are not accompanied by adhesions (Fig 709) The average diameter of 312 tumors in Dockerty s series was 6 cm. The tumor is grayish white and may contain focal yellow areas of fatty degeneration These areas may become cystic. Ninety per cent of these tumors are unilateral. They are not malignant Differentiation from thecoma may be impossible inasmuch as some fibromas are undoubtedly inactive thecomas. Krukenberg tumors also superficially resemble thecomas but almost invariably are bilateral. Microscopically fibromas appear to be an overgrowth of ovarian stroma. These connective tissue cells are often closely packed and arranged in a "feather stitched pattern (Fig 710) There may be hyaline bands such as seen in thecomas and considerable edema between tumor cells may be present.

Clinicopathologic Correlation.—In Dockerty s group 51 of the 283 patients with fibroma had ascites Ascitic fluid usually is a transudate. Infrequently the ascites may be associated with pleural effusion (Meigs) When both ascites and pleural effusion are present a diagnosis of inoperable ovarian neoplasm often is made, but after removal of the tumor both of these complications disappear The mechanism of pleural effusion has been demonstrated by Meigs The intrathoracic negative pressures are thought to account for the transdiaphragmatic passage of fluid through pleural peritoneal "pores" or lymphatics Flow from the pleural cavity into the abdomen apparently does not take place. Other tumors also may cause this syndrome (Meigs)

Endometrial Carcinoma

Samson was the first to report an adenocarcinoma of the ovary arising from an endometrial cyst. He proposed the following criteria (1) coexistence of benign and malignant tissue in the same ovary with the same histologic relation to each other as in carcinoma of the body of the uterus and (2) carcinoma must actually appear to be arising in the tissue not invading it. Additional supporting evidence includes the presence of tissue resembling endometrial stroma around characteristic epithelial glands and the finding of old rather than fresh hemorrhage This malignant tumor is rare according to Greene there are only 24 cases reported. Adenoacanthoma can arise in an area of endometriosis (Kistner)

Novak states that there is no reason to be surprised by the origin of carcinoma from ectopic endometrium because it exhibits the same biologic reactions as does

that of endometrium located in the uterine mucosa. Ectopic endometrium may exhibit marked secretory changes or hyperplasia of typical "Swiss cheese" type.

Metastatic Carcinoma (Krukenberg Tumor)

Metastatic carcinoma of the ovary is called Krukenberg tumor. This designation has perhaps obscured the understanding of it. This eponym should be

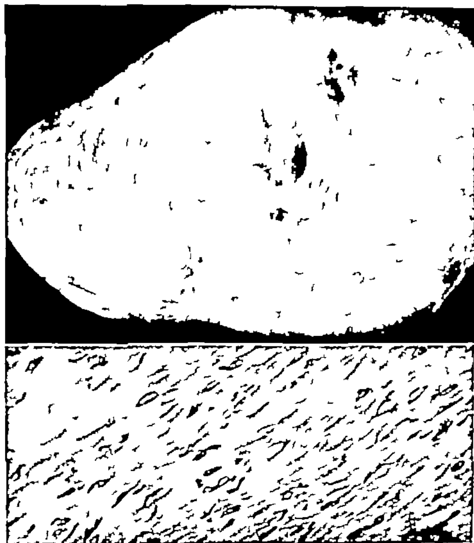


Fig. 709.—Gross photograph of a large fibroma of the ovary. (W U neg 50-4914.) (Specimen contributed by Dr John Saxton, St Louis City Hospital, St. Louis, Mo.)

Fig. 710.—Photomicrograph of a fibroma with well-differentiated fibroblasts separated by a hyaline stroma. (×360.) (W U neg 50-5218.)

discarded because these tumors are always metastatic (Leffel). They are almost invariably bilateral. The individual tumors usually are of moderate size, fairly firm, and have a smooth capsule (Fig. 711). On section they may have small areas of cystic and mucinous change. The tumor probably reaches the ovary through the lymphatics. Krukenberg tumors incident to carcinoma of the stomach always have associated retroperitoneal lymph node metastases. cells probably

travel in a retrograde fashion from the stomach to the ovary via retroperitoneal lymph nodes and ovarian lymphatics Peritoneal implantation also occurs but Krukenberg tumors are not seen in the absence of retroperitoneal lymph node involvement Microscopically the ovaries are replaced by tumor frequently the nuclei are compressed by mucin (signet ring appearance) (Fig 712) There is usually diffuse overgrowth of fibrous tissue which may obscure the diagnosis Mucin stains often are helpful in these instances We have seen this tumor incorrectly diagnosed as a granulosa cell neoplasm



Fig 711 —Gross photograph of bilateral metastatic carcinoma of the ovary (Krukenberg tumor) appearing in a young woman. (W U neg 52 563)

Fig 712.—Photomicrograph of signet ring cells in a metastatic carcinoma. (Krukenberg tumor) of the ovary (×540) (W U neg 5? 140)

Clinicopathologic Correlation—Ovarian metastases frequently occur as a Krukenberg tumor in women about 40 however we have seen several in women under 30 The ovaries of younger women have a much better blood and lymphatic supply The primary lesion usually is gastrointestinal it most often is gastric. Stone summarized 133 cases of secondary ovarian carcinoma 102 were primary in the stomach and intestine The origin may also be from the pancreas or the gall bladder Of 41 Krukenberg tumors carcinoma of the breast was as frequent a source as gastrointestinal carcinoma (Warren) Young women with carcinoma of the breast undergoing surgical castration often are found to have ovarian metastases

PROGNOSIS

Unfortunately the over all five year survival rate of patients with malignant ovarian tumors is extremely poor Munnell reviewed 200 primary tumors of the ovary seen at the Sloane Hospital for Women, he emphasized that 60 per cent of the patients had a hopeless prognosis and died within the first year and a half. After 18 months the rate of dying slowed so that during the next five years only 10 or 12 per cent expired This mortality probably is related to the lack of symptoms during the early stages of these tumors and to their rather rapid growth rate. The most important signs and symptoms include lower abdominal pain abdominal enlargement and signs of increased pressure on neighboring organs The prognosis is influenced by the type of tumor (Table 30) Dysgerminomas, granulosa cell tumors, and arrhenoblastomas have a low malignant potential and often are cured. Unfortunately they make up but a small proportion of ovarian tumors. There is a direct correlation between the grade of the serous tumors and the prognosis similarly some correlation also exists with grading of mucinous tumors. The most important pathologic finding is spread of tumor beyond the ovary This spread frequently is associated with ascites, which makes the prognosis more unfavorable. The solid tumors generally are more malignant than the cystic ones.

TABLE 30 MALIGNANT POTENTIAL OF OVARIAN NEOPLASMS

BENIGN	LOW	HIGH
Fibroma	Arrhenoblastoma	Carcinoma, unclassified
Thecoma	Dysgerminoma	Malignant teratoma
Brenner	Granulosa cell tumor	Serous cystadenocarcinoma
Cystic teratoma	Mucinous cystadenocarcinoma	Pseudomucinous cystadenocarcinoma
	Serous cystadenocarcinoma	

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PLACENTA

HYDATIDIFORM MOLE AND CHORIOCARCINOMA

Hydatid moles are tumors of the placenta (not of the uterus) which complicate pregnancy and occur as grapelike masses of cysts These cysts are products of degeneration of the stroma in the villi (Figs. 713 and 714) It is imperative that careful microscopic study of hydatid moles be made (at least ten sections) for evidence of choriocarcinoma. Examination of the curettings is particularly important. If they show no tumor the prognosis is good. Undoubtedly hydatidiform moles are incorrectly diagnosed as carcinoma much more frequently

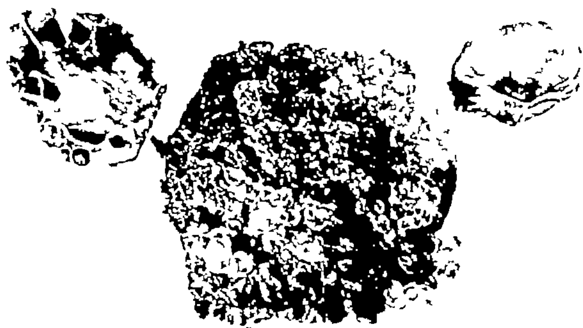


Fig. 713 —Classic example of hydatid mole almost obscuring the wall of the uterus. Note changes in ovaries. (Courtesy Dr Margaret Carter Houston, Texas.)

than carcinoma is incorrectly diagnosed as hydatidiform mole. Unnecessary hysterectomy is the result. The more malignant a hydatid mole appears microscopically the greater the chance of choriocarcinoma. Invasion of the stroma of the mole is a particularly bad sign. No matter how malignant a mole appears the diagnosis of choriocarcinoma cannot be made. The sections of the mole naturally cannot determine what is in the uterine wall This is further complicated by the fact that trophoblasts normally invade blood vessels and reach the lung where they die (Novak) They may invade the myometrium this is best termed syncytial deciduitis and is not a neoplasm. During normal pregnancy invasion of

Fig 714 —A rather hyperplastic villus in a hydatidiform mole This was interpreted as completely benign. (×220) (W U neg. 50-3843)

Fig 715 —Photomicrograph of normal trophoblastic invasion of the uterine wall at the implantation site in pregnancy These changes may be misinterpreted as choriocarcinoma. (×310) (W U neg 58-4206.)

uterine musculature may occur it is most pronounced in the area of implantation (Fig 715) These changes are maximal during the first two months of pregnancy Sections of the implantation area may be mistaken for choriocarcinoma

Hertig classified moles into several subvariants of little practical importance, for in 200 patients with hydatid moles, 5 had choriocarcinomas, and these were the only patients who died. Chorioadenoma destruens is an invasive mole which may extend through the myometrium into the broad ligament, invade veins, and even

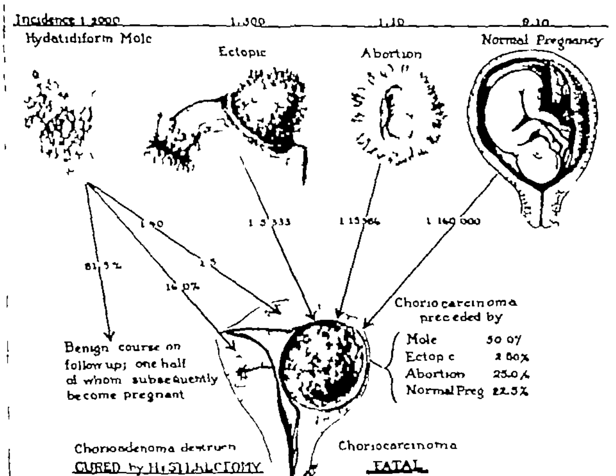


Fig 716 —Origin and incidence of choriocarcinoma. (Courtesy Dr Arthur T Hertig Boston Mass., published in Meigs J V and Sturgis S H. (editors) Progress in Gynecology New York, 1950 Grune & Stratton Inc.)

cause uterine rupture. Hodgkinson reported a case in which the Friedman test was positive up to the time of uterine perforation The patient remained well after hysterectomy In the past this lesion was always considered to be a highly invasive mole not a choriocarcinoma. This diagnosis was based mainly on the presence of persistent chorionic villi We have now learned that chorionic villi may rarely be present with choriocarcinoma discrete differentiation between invasive mole and choriocarcinoma is not possible We have seen four cases with villi present in both the primary tumor and the fatal pulmonary metastases (two of these patients were from Indonesia, one from the Philippines, and one from the United States) (Tjokronegoro, Barrera)



Fig. 717.—Gross photograph of uterus and vagina showing large masses of hemorrhagic choriocarcinoma within the uterus and metastatic to the vagina. (W U neg 49-3585)

Choriocarcinoma occurs in only one of 14 000 pregnancies and causes one fatality in 26 000 pregnancies (Park) It can occur after one missed menstrual period or after a full term pregnancy (Fig 716) There is a high incidence of both hydatidiform mole and choriocarcinoma in China the Philippines and Indonesia The cause for this remains unexplained Grossly the uterus is enlarged and the tumor within it forms coalescing hemorrhagic necrotic masses (Fig 717) This characteristic necrosis and hemorrhage may be so extreme that only a small rim of gray friable tumor tissue can be identified Destruction of the myometrium is common and rarely it may masquerade as a hydatidiform mole



Fig 718—Photomicrograph of choriocarcinoma in a large vein within the uterus. Cytotrophoblasts predominate The patient had pulmonary metastases and died of choriocarcinoma. (×420) (W U neg 52 2573)

The characteristic nodules of choriocarcinoma are dark purple and vaginal implants are common. Microscopically the usual lesion is formed by islands of cuboidal to round cells with pale nuclei which are derivatives of the Langhans cells. These groups of cells are surrounded by cells which have dark-staining nuclei of various shapes and sizes arranged in a syncytium. These cells are the derivatives of the syncytial cells of the villus. If this pattern is present the diagnosis is not difficult All possible variants can occur (Novak) (Figs. 718-721) The lesion can show predominance of Langhans cells or syncytial cells. Tjokronegoro emphasizes the constant presence of necrosis hemorrhage, and inflammation in choriocarcinoma. The presence of villi used to be considered as evidence that the lesion was benign but we have already cited exceptions to this rule (Fig 722)

Quantitative serum assays for chorionic gonadotrophin are elevated in patients with hydatidiform moles. It is not generally realized how long such tests may remain strongly positive. Delfs found such assays negative by the sixtieth day in 31

of 41 patients with mole (75 per cent) 5 others showed continuing decline in the level of chorionic gonadotrophin

It must be remembered that biologic tests assess only the presence of trophoblastic tissue, not the presence of choriocarcinoma, and that high gonadotrophic excretion occurs about the sixtieth day of normal pregnancy (Boycott) At times there may be little or no excretion of gonadotrophin from hydatidiform mole metastatic choriocarcinoma may be associated with a lower level of gonadotrophin than in a normal pregnancy (Fluhmann)

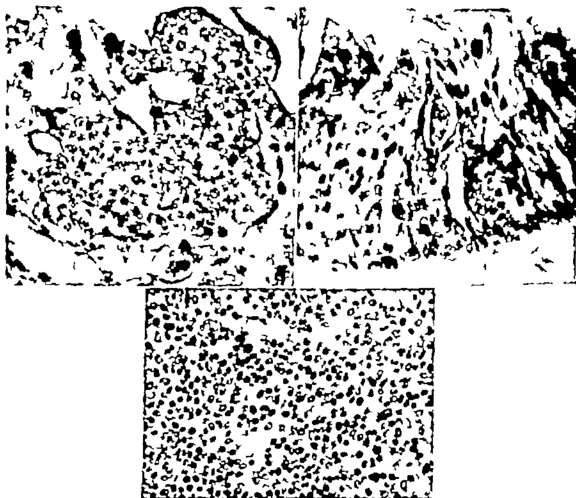


Fig 719 —Typical choriocarcinoma showing islands of Langhans cell derivatives surrounded by the larger pink-staining syncytial cells. (×400) (W U neg 54-5834 Case N50303)

Fig 720 —Choriocarcinoma formed predominantly by syncytial cells. The patient was a 35-year-old Indonesian woman who had had a hysterectomy thirteen months following removal of a hydatidiform mole Vaginal metastases with identical histologic pattern appeared twelve months after operation. Pulmonary metastases were demonstrated fourteen months after operation. (×400) (W U neg. 54-5835 Case 46534)

Fig. 721 —Choriocarcinoma formed principally by Langhans cells. The patient, a 23 year-old Indonesian woman, had a hysterectomy two months following the onset of uterine bleeding The sections showed typical choriocarcinoma in other areas. The patient is being followed at monthly intervals, and was well with negative gonadotropin tests eight months following operation. (×400) (W U neg 54 5837 Case 50977)

(Slides for Figs. 719-721 contributed by Dr S. Tjokronegoro Jakarta, Indonesia.)

The clinical course of choriocarcinoma is unpredictable Spontaneous regression even of metastatic lesions, may take place (Teacher) The chances of such regression are greatest when chorionic villi are found in the primary tumor (Fig 722) Maier reported an unusual instance of choriocarcinoma occurring in the lung two and one half years after passage of a hydatidiform mole. This patient died five years after lobectomy of metastatic choriocarcinoma in the brain

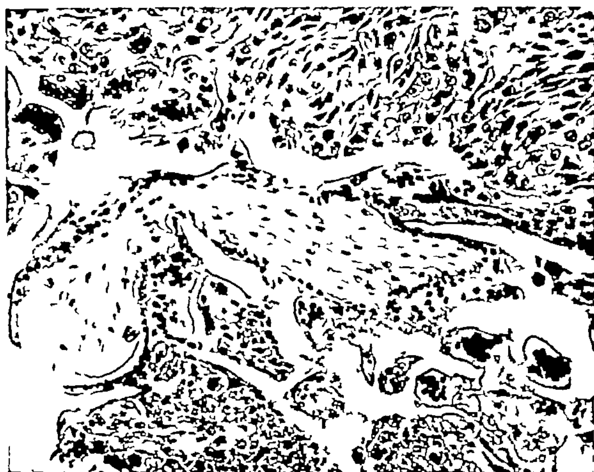


Fig 722.—Photomicrograph showing the presence of the chorionic villus which prompted an erroneous diagnosis of destructive mole. This patient died. There were also chorionic villi in the metastases. (×190) (W U neg 54 5842 Case 61147) (Slide contributed by Dr S Tjokronegoro Jakarta, Indonesia)

Occasionally choriocarcinoma is diagnosed with certainty only after the death of the patient. The pathologist s attitude should be a conservative one thereby many unnecessary hysterectomies will be avoided Hysterectomy probably salvages few patients with choriocarcinoma by the time diagnosis is made distant metastases to the lung and brain are probably present. Choriocarcinoma usually causes death within six months

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Chapter 18

BREAST

INTRODUCTION

The breast is the most important organ from the standpoint of surgical pathology because of the frequency of both benign and malignant breast lesions.

Carcinoma of the breast is the most common carcinoma encountered in New York State excluding New York City (Levin) Whether a lesion is benign or malignant is usually the problem faced by both the pathologist and surgeon This decision may be quite difficult, but must be resolved before therapy can be instituted.

METHOD OF EXAMINATION

The examination of a radical mastectomy specimen should be thorough much information may be gained by meticulous study The specimens submitted by different surgeons in large general hospitals may vary widely A radical mastectomy must include adequate skin all breast parenchyma, the underlying and surrounding fat the pectoralis major and minor muscles and the axillary contents in continuity and en bloc. Specimens which do not contain the pectoral muscles or which include only half hearted dissections of the axillary contents are not radical mastectomies and should not be so designated by the pathologist. At operation the surgeon should tag the high point of the axillary contents as he removes it from about the medial extreme of the axillary vein. This allows the pathologist to orient the specimen. Evidence of edema and ulceration of the skin surface should be noted. If a mass is felt, its borders should be measured. At least three sections should be taken from the tumor with an attempt to include underlying muscle fascia, and overlying skin if they appear involved It is our custom to section all breast quadrants particularly the most prominent parenchymal areas for such sections may show unexpected extension of the tumor multiple foci of origin, or various proliferative and possible precancerous lesions.

The most complete method of examining the axillary contents is to clear the axilla and section each node serially Such a study is obviously too time consuming and financially extravagant to be used routinely Saphir studied 30 cases of carcinoma of the breast with apparently negative axillary lymph nodes. By serially sectioning the nodes he discovered that 10 of the 30 actually had axillary metastases However the number of nodes found in his series totaled only 149 an average of less than 5 nodes per specimen. In other words, the 30 cases had not had adequate initial node examination The necessity for serially sectioning the nodes is obviated by thorough search of the axillary contents for nodes with single sections of each node An average of at least 25 axillary nodes can thus be examined (Table 31)

TABLE 31 NUMBER OF LYMPH NODES FOUND IN AXILLA

YEAR	NUMBER OF NODES FOUND	NUMBER OF CASES	AVERAGE NUMBER OF NODES
1944	833	41	21.5
1945	900	32	28.1
1946	1 192	51	23 4
1947	1 103	41	26 9
	4 078	165	25 4

We divide the axillary contents arbitrarily into high mid, and low areas. By studying the fresh material in a strong light one can see and feel the small gray nodes even 0 2 cm. in diameter against the glistening yellow fat. Small nodes

missed by superficial study may contain carcinoma. The number and distribution of involved nodes in the axilla bear a relationship to prognosis.

In Monroe's study of 87 radical mastectomy specimens the axilla was cleared and all nodes sectioned, the variable numbers of nodes per specimen were thought to be related to the different surgical techniques used. He found an average of 30.4 lymph nodes per specimen and as many as 65 in a single breast. Eleven of the most radical dissections contained an average of 46.3 lymph nodes. We do not believe the extra time necessary to clear a specimen justifies the information gained.

The final step in the examination of the specimen is to place sections of the main tumor, the three other quadrants, and the lymph nodes from the high, mid and low areas of the axilla into seven separate bottles. While this procedure is time consuming to both pathologist and technician, the information gained is worth while, particularly from the standpoint of prognosis. Decision concerning post-operative roentgen therapy will be influenced by the adequacy of this examination and whether or not the lymph nodes contain cancer.

FROZEN SECTION

In our institution, radical mastectomy is practically never done without a histologic diagnosis. In a few instances where the clinical findings are obvious, needle biopsy before surgery is diagnostic. In most instances at the time of operation the surgeon requests a frozen section. If the lesion is small (2.5 cm. or less) it is entirely excised. If it is larger, then careful incisional biopsy is the best procedure. Incisional biopsy is preferable for large lesions because it disturbs the tumor bed the least. Frozen section diagnosis is accurate. In our last 440 frozen sections there were no false positives and 4 false negatives. In 10 instances, although there was a strong suspicion of cancer, the diagnosis was deferred for the permanent sections. Eight of these cases proved to be cancer. There is no evidence that waiting for the results of the permanent sections (24 hours) causes harm. The greatest difficulty is encountered with papillary lesions, intraductal cancers, and sclerosing adenosis (Figs. 723 and 724). Both the surgeon and pathologist should take great precaution to avoid an erroneous diagnosis of cancer which will result in an unnecessary radical mastectomy.

INFLAMMATORY LESIONS OF THE BREAST

Abscess

With the advent of chemotherapy suppurative mastitis during lactation is no longer common. Grossly abscesses form and in the nearby breast parenchyma chronic inflammation with duct stasis and obliteration of lobular pattern is usually present. Microscopically all signs of inflammation are present; plasma cells usually are abundant.

Tuberculosis

Tuberculosis of the breast is rare and invariably is secondary to blood stream dissemination or invasion from an adjacent tuberculous process. Grossly advanced



Fig 723 —Photomicrograph of well-differentiated carcinoma of breast, diagnosed by frozen section. Patient was a young woman with a single nodule clinically thought to be benign. (×165) (W U neg 49 4436.)

Fig 724 —Radical mastectomy demonstrated carcinoma in other quadrants and in one axillary lymph node. Tumor in this section is from a quadrant remote from the primary tumor (×195) (W U neg 49-4437)

tuberculosis of the breast has suppurating multiple sinuses and areas of necrosis and caseation This lesion may be mistaken clinically for advanced breast cancer The regional nodes are quite often involved in caseating forms of tuberculosis In these instances radical mastectomy may be necessary, usually simple mastectomy is adequate

Plasma Cell Mastitis

Plasma cell mastitis is a rare lesion only about 50 cases have been reported (Adair) We have not seen this lesion during the past ten years. Grossly there is often extensive edema of the breast duct stasis and interstitial induration Multiple areas of fat necrosis also accompany the tumor We have seen this lesion associated with underlying carcinoma of the breast (Halpert) Rarely it is bi lateral Microscopic examination shows duct stasis focal areas of fat necrosis and invariably a widespread interstitial infiltrate consisting almost entirely of plasma cells. The interstitial infiltrate is thought to be due to the chemical effect of decomposing fat ductal contents. Clinically there may be a history of trauma The edema firmness and tenderness frequently suggest a diagnosis of carcinoma The average age of the patient with plasma cell mastitis is between 35 and 40 years (Cutler) If the lesion is purely inflammatory local excision is indicated Regional nodes also may be enlarged by inflammatory infiltration It should be remembered that carcinoma may be associated with the plasma cell mastitis

FAT NECROSIS

Fat necrosis of the breast usually occurs in obese patients with pendulous breasts. The lesion was described well by Lee and Adair in a number of articles dating from 1920 Adair (1947) reported its incidence to be 2 76 per cent of the patients with primary operable carcinoma. There may or may not be a history of preceding severe trauma 62 of 110 cases had no trauma (Adair 1947) Localized areas of fat necrosis in the breast may develop after excision of a mass Subcutaneous involvement overlying the breast may be only a localized manifestation of Weber Christian disease (relapsing febrile nodular nonsuppurative panniculitis) (Binkley)

Grossly the lesion may be in the subcutaneous tissue or in the breast. When it is located within the breast it measures from 1 to 8 cm. is firm but not stony hard, rather sharply defined and at times occurs as multiple masses. The gross appearance is sufficiently characteristic to differentiate it from carcinoma. Early fat necrosis is confined to several well-defined fat lobules later the lesion may become cystic. These cysts may be small or large they contain yellow granular material and pools of fat. The firmer areas may be opaque, yellowish-brown, and greasy There is considerable surrounding fibrous induration These cystic areas may eventually develop calcareous masses

Fat necrosis is nonbacterial it is caused by slow aseptic saponification of nodular fat by blood and tissue lipase (Hadfield) Microscopically there may be fat filled cystic spaces surrounded by foreign body giant cells, collections of fat filled macrophages and interstitial infiltration by plasma cells. Duct stasis is uniformly present this finding is probably related to pathogenesis (Foote) Inter



Fig 725 —Retraction of the skin in a patient with fat necrosis. (W U neg 50-2035) (From Lee B J and Adair F: Ann. Surg 80 670 1924)



Fig. 726 —Photomicrograph of duct stasis with fat necrosis and plasma cell infiltration This patient had retraction of the nipple and an indefinite mass. There was no carcinoma. (×225) (W U neg 51-4?12.)

stitial tissues may also show an increased number of plasma cells The prominent proliferation of the connective tissue around the lesion may cause it to be confused with a malignant neoplasm

Clinicopathologic Correlation

The firm lesions of fat necrosis more closely mimic carcinoma than any other benign lesion of the breast Over half the lesions are attached to the overlying skin, but the nipple seldom is retracted and deep attachment is rare (Fig 725) Breast pain and axillary lymph node enlargement are usually absent The close clinical resemblance of this lesion to carcinoma is emphasized by Hadfield 12 of 45 cases reviewed had radical mastectomy for supposed cancer

Of 12 consecutive cases of fat necrosis in the Barnes Hospital (before 1948) 5 were thought to be carcinoma 2 of the patients had a radical mastectomy Haagensen reported cases of *mammary duct ectasia* a lesion described under names such as comedomastitis In this process there is dilatation of the ducts fibrous thickening of the walls and ductal accumulation of fatty detritus (Fig 726) When this material escapes from the ducts it causes considerable inflammation. Ductal thickening and shortening may be associated with retraction of the skin and nipple resulting in a clinical diagnosis of carcinoma.

We have been impressed by the similarity between plasma cell mastitis fat necrosis, and mammary duct ectasia. We believe they are varying degrees of the same process. Duct stasis is the common denominator in all of them If the material escapes from the ducts fat necrosis may result Inflammatory reactions invariably contain innumerable plasma cells.

CHRONIC CYSTIC DISEASE

Two questions frequently asked concerning chronic cystic disease are (1) Does chronic cystic disease predispose to carcinoma? (2) Does carcinoma arise from areas of chronic cystic disease? It is very difficult to answer these questions dogmatically Frantz studied the incidence of chronic cystic disease in 225 women at the time of postmortem examination. To summarize her findings The incidence of chronic cystic disease similar to that occurring in surgical specimens was exceedingly low In fact she found only one instance of a cyst large enough (2 cm.) to have constituted a dominant lump The incidence of chronic cystic disease found in these breasts was significantly lower than in cancerous breasts

By contrast, proliferative changes are frequently found by careful examination of breasts containing carcinoma. In some instances histologic transition to carcinoma can be traced from proliferative lesions from areas of hyperplasia in acinar epithelium from epithelial proliferation within a cyst and from apocrine epithelium (Fig 727) Haagensen s study showed that a group of patients with chronic cystic disease had four times greater risk of developing cancer than a similarly aged group without it (Table 32)

Foote demonstrated that a patient with chronic cystic disease primarily in one breast has just as much chance of developing cancer in the opposite breast. Therefore the only rational form of prophylactic treatment would be to remove

both breasts. The only procedure indicated for the increased frequency of carcinoma in chronic cystic disease is a close follow up particularly of premenopausal women.

Table 32 Chronic Cystic Disease and Cancer*

Age	Years at risk	Expected no. of cancers	Number
20-39	341	102	
40-49	985	800	3
50-59	676	773	5
Over 60	160	283	
		1 96	8

*Compiled from Haagensen, C. D Diseases of the Breast Philadelphia, 1956, W. B. Saunders Co.



Fig 727 —Photomicrograph of excessive proliferation of apocrine epithelium in a breast with carcinoma in another quadrant. (×150) (W U neg 52 2474)

Chronic cystic disease is extremely important in surgical pathology Because it is proliferative it often is confused with carcinoma. Its incidence is difficult to estimate because the diagnosis depends upon the liberality of the individual pathologist (Foote) It is most common in patients between 25 and 45 years of age.

Chronic cystic disease has all gradations of severity The cysts have a bluish cast (blue dome cyst of Bloodgood) and contain cloudy yellow or clear fluid The breast parenchyma between the larger cysts is yellowish-gray and may contain numerous small thin walled cysts (Fig 728) Large cysts are relatively infrequent. The process is most commonly bilateral but one breast may be much more diseased than the other and appear clinically to be the only one involved. At times no cysts are present there is only diffuse fibrous thickening of the parenchyma.

Fig 728.—Gross photograph of chronic cystic disease demonstrating a large smooth walled cyst, multiple small cysts and increased stromal components (W U neg 52 5340)

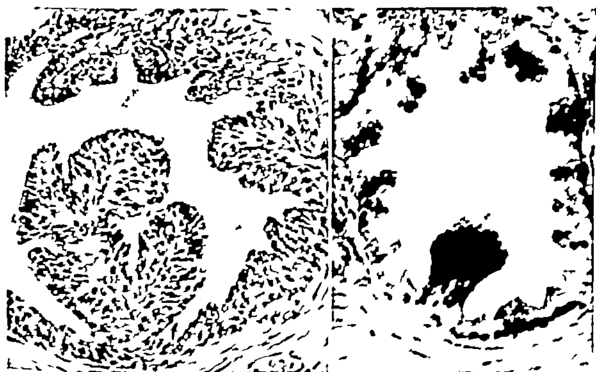


Fig 729 Photomicrograph of a microscopic area of intraductal papillomatosis This type of lesion is common in chronic cystic disease (×210) (W U neg [illegible])

Fig 730 Photomicrograph of proliferative apocrine epithelium in a patient with chronic cystic disease (×120) (W U neg 48-4717)



Fig. 731 —Photomicrograph of an area of sclerosing adenosis. Note distortion and poor delineation caused by the fibrous tissue proliferation. (×200.) (W U neg 49 4500.)

Fig 732 —Photomicrograph of the same lesion shown in Fig 731 to show absence of necrosis, uniformity of cells and lack of mitotic activity (×400.) (W U neg 49-4501.)

Microscopically the proliferative changes vary The walls of the cysts usually are lined by flattened epithelium this epithelium may be completely absent the cyst having only thick fibrous walls The breast parenchyma of true cystic disease invariably contains patches of apocrine epithelium which may have a papillary pattern (Fig 730) The individual cells are large with well-defined nuclei and bright pink cytoplasm Multiple areas of microscopic intraductal papillomatosis are common (Fig 729) There also is considerable proliferation of the acinar epithelium the pattern being modified by the accompanying connective tissue proliferation In time the connective tissue proliferation may become acellular and hyalinized With this change individual breast lobules invariably are distorted this may be sufficient to be misdiagnosed as invasion The ducts may proliferate and have blind endings this change has been designated by Foote as blunt duct adenosis. It is this melange which makes the entity chronic cystic disease

Sclerosing Adenosis

Sclerosing adenosis is merely a rather uncommon highly proliferative form of chronic cystic disease It is found about once in every 100 benign breast lesions In a large series reported by Urban the average age of the patient was 31 years (20 to 50 years) The process usually occurs in the upper outer quadrant (the most common site of carcinoma of the breast) has disclike configuration and cuts with increased resistance The thickened parenchyma of most cystic disease cuts smoothly and does not show any areas of necrosis such as seen in breast carcinoma. Sclerosing adenosis causes the pathologist great anguish at frozen section because it may simulate malignant invasion. Permanent sections too may be difficult to interpret the absence of necrosis the persistence of lobulation, and the knowledge that connective tissue proliferation may distort the pattern should allow the correct diagnosis to be made (Figs. 731 and 732) Mitotic figures may appear in these lesions and should not be interpreted as evidence of carcinoma.

BENIGN NEOPLASMS

Fibroadenoma

Fibroadenomas of the breast are common in women between 20 and 35 years of age. These tumors increase in size during pregnancy and tend to regress as the age of the patient increases Grossly they are usually single but may be multiple in the same breast or in both breasts. In the younger age group a type of fibroadenoma (fetal) may weigh as much as 1 000 grams (Figs 733 and 734) The usual fibroadenoma, however is a sharply demarcated firm tumor usually no more than 3 cm. in diameter In time it may calcify or ossify and become extremely hard. Rarely in the younger women an adenoma may undergo partial or complete mucoid degeneration The cut surface is grayish white with a whorllike pattern in which poorly defined nodules project slightly above the cut surface (Fig 735) The intracanalicular type may have slitlike spaces necrosis is absent The absence of necrosis is valuable diagnostically the infrequent circumscribed type of breast cancer which is occasionally mistaken for fibroadenoma invariably has minute areas of necrosis.

Microscopically there is in the pattern of the fibroadenoma great variation because of different amounts of the epithelial and connective tissue components Fibroadenomas are labeled intracanalicular when the growth of connective tissue is so rapid that it invaginates the ducts into slitlike spaces (Fig 736) Such changes may be prominent or nearly absent. The well-defined glands have cells

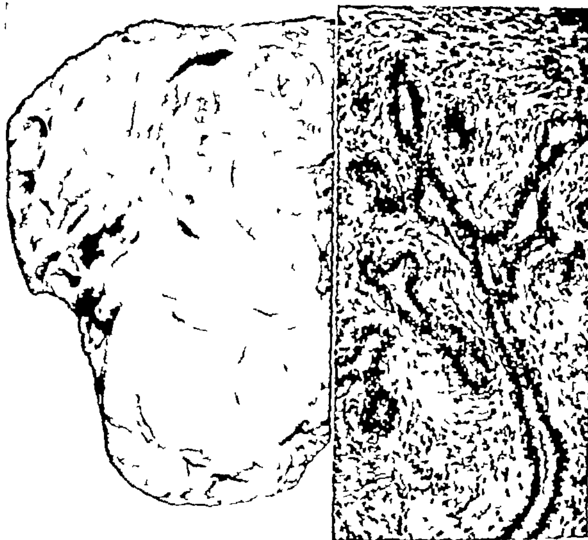


Fig 733 —Gross photograph of a large lobulated fetal type of fibroadenoma occurring in a Negro woman 37 years of age. Note absence of necrosis. (W U neg 51 5002.)

Fig 734 —Photomicrograph of fetal type of fibroadenoma with cellular stroma and well-defined glands. (×150) (W U neg 49-5941)

with uniform nuclei The stroma may be quite cellular During lactation, adenomas have been described but we believe that they merely represent accentuation of a normal process Infrequently distortion of lobules results in a mistaken diagnosis of cancer (Gill) Fibroadenomas rarely become malignant, but if they do, they are sarcomas (see p 717) There have been cases in which the epithelial element of a fibroadenoma has become neoplastic (Austin) but these instances are extremely rare and usually represent secondary invasion of a carcinoma from neighboring breast parenchyma.

Intraductal Papilloma

The intraductal papilloma is one of the most important lesions arising from the ducts of the breast. The treatment of these lesions has included no treatment



Fig. 735 —Gross photograph of the usual fibroadenoma, grayish white in color projecting slightly above the cut surface (W U neg 48-4541)

Fig. 736 —Photomicrograph of an intracanalicular adenofibroma with rather cellular stroma. (Low power) (W U neg 47 102)

local excision, simple mastectomy, and radical mastectomy The inexperienced pathologist frequently incorrectly diagnoses them as carcinoma. Table 33 indicates their benign character their distribution and the results of treatment.

TABLE 33 FOLLOW UP OF 76 PATIENTS WITH INTRADUCTAL PAPILLOMA TREATED BY LOCAL EXCISION—PRESBYTERIAN HOSPITAL, 1916-1941*

SITE IN BREAST	TOTAL CASES TREATED BY LOCAL EXCISION	RECURRENCE OF PAPILLOMA		DEVELOPED CARCINOMA	PER CENT FOLLOW UP
		UNDER 5 YR.	AFTER 5 YR.		
Central	56	2	0	0	94 6
Peripheral	20	0	1	0	95 0
All sites	76	2	1	0	94 7

*Compiled from Haagensen C D., Stout A P., and Phillips, J S Ann Surg 133: 18 36 1951

These lesions can usually be palpated when they are in the region of the nipple. They are often small but may become 4 or 5 cm. in diameter (Fig 737) They usually are quite soft and fragile, being supported only by filamentous fibrous tissue trabeculae. Areas of hemorrhage are common. The larger ones appear to

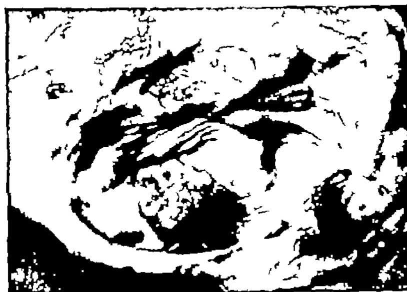


Fig 737 —Gross photograph of a soft, rather large intraductal papilloma. (W U neg. 47 3569)

lie inside a cystic dilatation of the duct. The multiplicity and the danger of malignant change of these lesions have been grossly exaggerated. Haagensen reported recurrences in only 3 out of 108 instances. These recurrences may have represented new lesions but in any event the disease did not progress We have seen rare benign papillomas of the nipple.

Microscopically frozen section of the intraductal papilloma often is difficult because of its extreme cellularity (Fig 738) The papillary projections may be trapped in the wall of the cyst, suggesting invasion and malignancy Infarction and squamous metaplasia may be difficult to interpret. The lesion which is extremely cellular and highly vascular is too often called carcinoma.

The difficulty in diagnosis increases with the size and complexity of the papilloma If a major duct contains a papilloma local excision is adequate therapy Long term follow up without the development of further difficulty emphasizes the wisdom of conservative treatment (Snyder Madalin) Simple mastectomy is not indicated



Fig. 738 —Photomicrograph of a rather cellular intraductal papilloma supported by a vascular connective tissue stalk. There is no evidence of malignant change. (×400)

Gynecomastia

Gynecomastia can result from innumerable causes Wheeler reported 160 cases and emphasized that enlargement of the male breast before 25 years of age usually was related to puberty but after 25 it was often a manifestation of serious underlying disease Gynecomastia is characterized by considerable epithelial intra ductal hyperplasia, and areas of stromal edema (Fig 739) This swollen stroma around ducts produces the "halo effect associated with the diagnosis gynecomastia. To quote Fisher

> The periductal stroma in gynecomastia contains an increase in ground substance over that noted in the normal male breast. This substance has been characterized as hyaluronic acid by the histochemical procedures employed in this study This same mesenchymal mucopolysaccharide is also present in fibroadenoma of the female breast. The ground substance of the periductal stroma in gynecomastia is similar to

that noted in other connective tissue areas responding to hormonal stimulation particularly estrogens. Such a similarity offers demonstrable evidence for the well recognized clinical association of gynecomastia with certain endocrine disorders and the diseases influencing the endocrine system either in a relative or absolute manner

Rarely these cases show such extreme intraductal epithelial hyperplasia that they are mistaken for carcinoma. Infant breast tissue may also show intraductal hyperplasia and stromal alterations (Steiner) Similar changes occur in patients

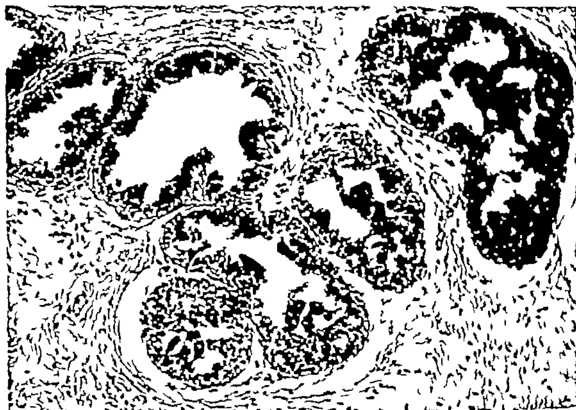


Fig 739 —Photomicrograph of prominent intraductal hyperplasia and stromal edema in gynecomastia. (×145) (S P 56-4822.)

who have received large amounts of stilbesterol and estrogen for breast cancer or for carcinoma of the prostate. In a male patient who develops a choriocarcinoma there are painful swollen breasts which also show intraductal hyperplasia and stromal edema. Chorionic gonadotropin acts by stimulating the testes, probably through the Leydig cells with excessive elaboration of androgenic and estrogenic hormones accounting for the enlargement and tenderness of the mammary glands. Karsner felt that lobulation did not occur but we have seen it in such patients (Mostofi) In Treves series of carcinoma of the male breast, nipple discharge was important there was no evidence of prior gynecomastia.

Granular Cell Myoblastoma

The histogenesis of granular cell myoblastoma is in doubt (Bangle) Grossly and clinically this rare lesion is often confused with carcinoma. On section it is firm, homogeneous, and usually white or grayish yellow As a rule it is not at

tached to the overlying skin, occasionally it is fixed to the underlying fascia. It may be as large as 10 cm. in diameter The occurrence of granular cell myoblastoma in the parasternal area suggests its possible origin from the skeletal muscle arising in this area Microscopically the tumor cells are uniform, large with well-defined nuclei, abundant granular cytoplasm and well-defined cytoplasmic outlines (Fig 740) Mitotic figures usually are not present, necrosis may occur at times. Sudanophilic material seldom is present in the tumor cells. Only frozen section will differentiate this tumor from carcinoma (Haagensen)

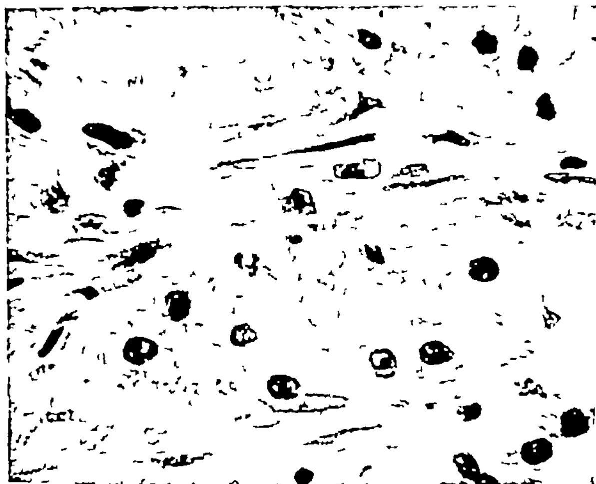


Fig. 740—Photomicrograph of granular cell myoblastoma of the breast. Note uniformity of nuclei and abundant granular cytoplasm. (×965) (S P 56-4822.)

MALIGNANT NEOPLASMS

Carcinoma

The overwhelming number of malignant tumors of breast parenchyma are carcinomas (95 per cent or more) These tumors arise from the duct and acinar epithelium. Their gross features are influenced by the variations in their growth within the ducts the amount of connective tissue and mucin they form, and their differentiation. Various names have been given to breast carcinoma, but these classifications are artefactual to a great extent. Classifications are of value only if they reflect important clinical diagnostic, or prognostic differences. The rela

tive frequency of various types of carcinomas is shown in Table 34. Extraneous adjectives which have no significance are often applied to breast carcinomas: scirrhous means hard, encephaloid means soft, and carcinoma simplex means a simple carcinoma. These titles are of no prognostic value.

TABLE 34

TYPE	RELATIVE INCIDENCE (APPROXIMATE PER CENT)
Arising from duct epithelium	
Carcinoma (no specific type)	75
Carcinoma plus Paget's disease	20
Comedocarcinoma	
Medullary carcinoma	
Acute carcinoma (inflammatory)	
Papillary carcinoma	
Mucinous carcinoma	
Epidermoid carcinoma	
Carcinoma, small cell type	
Arising from acinar or terminal duct epithelium	
Lobular carcinoma	5



Fig 741.—Gross photograph of a carcinoma of the breast with retraction of the nipple. There are fine grayish white streaks of tumor ramifying into the fat. (Courtesy Dr Richard Johnson, Ellis Fischel State Cancer Hospital, Columbia Mo.)

Grossly the usual carcinoma of the breast arising from duct epithelium is a poorly defined mass the hardness of which depends upon the age of the lesion and the amount of connective tissue present. *The tumor cuts with a resistant gritty sensation (unripe pear) is usually yellowish-gray and has fibrous trabeculae radiating through the bright yellow fat of the breast parenchyma* (Fig 741). It is not rare for these fibrous strands to connect with other nodules of carcinoma at some distance from the primary tumor. Predominantly cellular tumors are much softer and often contain larger areas of necrosis. The tumor may invade the underlying fascia or muscle. Microscopically the tumor cells vary in size and shape and may or may not form acini. The individual cells of a cellular tumor have prominent nucleoli and many mitotic figures. Areas of necrosis are common. It may be difficult to identify tumor cells if the connective tissue is greatly increased; they

may occur in groups of only five or six cells containing very little cytoplasm and surrounded by hyalinized connective tissue Under low power this infrequent variant of breast carcinoma (small cell type) may be completely missed (Fig 742) In younger women multiple foci of origin are not rare (Fig 743) Furthermore

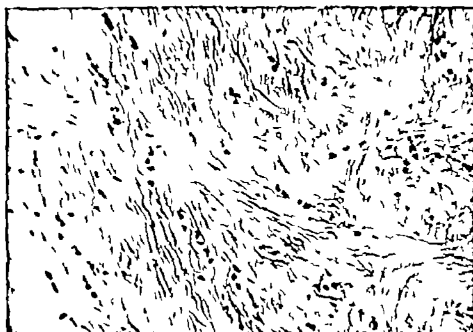


Fig 742 —Photomicrograph of a carcinoma of the breast (small cell type) with extreme production of fibrous tissue Only small nests of tumor cells are present (×200) (W U neg 49 5467)

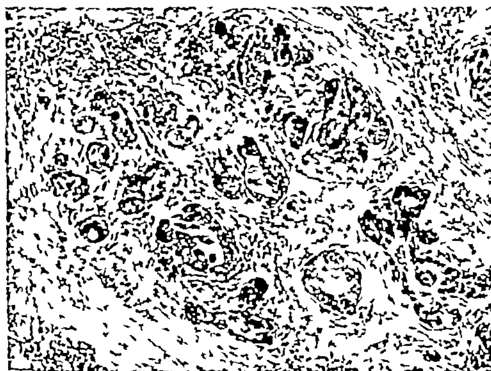


Fig 743 —Photomicrograph of cancerization of a lobule in a young female with carcinoma of the breast. This area of change was remote from the primary neoplasm (×150) (W U neg 49 5375)

Qualheim demonstrated that in whole-organ paraffin sections of breast carcinoma, multiple foci of origin occur commonly

Intraductal (Comedo-) Carcinoma.—Intraductal (comedo-) carcinoma is a relatively infrequent form of breast cancer which grows predominantly within ducts. The duct wall becomes greatly thickened largely because of increase in elastic tissue. Grossly the tumor contains thick walled ducts with normal breast



Fig. 744—Photomicrograph of intraductal carcinoma of the breast confined to the duct with central necrosis. (×180) (W U neg 50-687)

parenchyma between them. When the ducts are compressed, wormlike masses of necrotic tumor extrude from them thus the name comedocarcinoma. If the tumor is contained within the duct lumina and the duct walls are not too greatly thickened, tumor may not be recognized grossly Microscopically the tumor cells resemble those of the usual breast carcinoma in this instance however, the tumor cells are confined to the ducts and are apparently noninvasive. Individual tumor cells have nuclei of variable size and shape with numerous mitotic figures. There is very little supporting connective tissue, and areas of central necrosis are common (Fig 744) It should be stressed that carcinoma is designated intraductal only

when a large proportion of the tumor is within ducts. Even in these instances, the tumor may break through the duct wall and metastasize to regional lymph nodes. Any thought of simple mastectomy for such a lesion is inexcusable. The usual type of carcinoma (nonspecific type) may have occasional areas of tumor growing intraductally; such growth is not sufficient to justify a diagnosis of intraductal carcinoma.

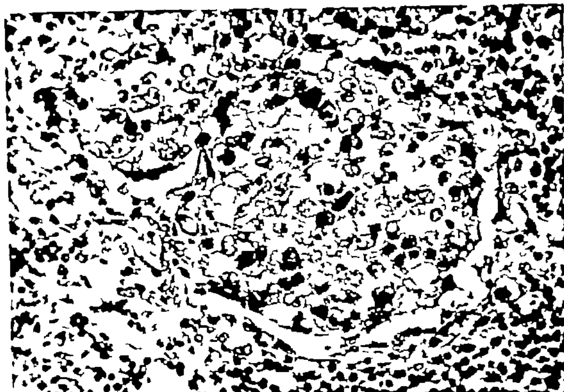


Fig 745.—Photomicrograph of a medullary carcinoma with considerable lymphoid stroma. Note poor differentiation of tumor cells (×400.) (W U neg 50-1419.)

Medullary Carcinoma.—The so-called medullary carcinoma of the breast has been well described by Moore. This lesion has a distinctive gross and microscopic pattern. Patients often are less than 50 years of age. The tumor frequently appears encapsulated and may be mistaken clinically and grossly for fibroadenoma. The tumors may attain a large size; they often are diffuse, homogeneous, gray, and contain small focal areas of necrosis. Microscopically the individual cells are rather uniform and have well-defined nuclei with numerous mitotic figures. An important part of the picture is a prominent lymphoid infiltrate (Fig 745). This type of lesion is often mistaken for lymphosarcoma microscopically. Patients with medullary carcinoma have a rather favorable prognosis (Richardson).

Paget's Disease Plus Carcinoma.—*Paget's disease* of the breast is a name given the crusted lesion of the nipple caused by cancer (Paget). It is merely a peripheral manifestation of an underlying carcinoma of the breast (Fig 746). Grossly these weeping eczematoid lesions appear to start on the nipple but later involve the areola and surrounding epidermis. They rarely extend more than a few centimeters. A palpable mass in the breast removed for Paget's disease may not be felt but almost without exception carcinoma will be found directly beneath the

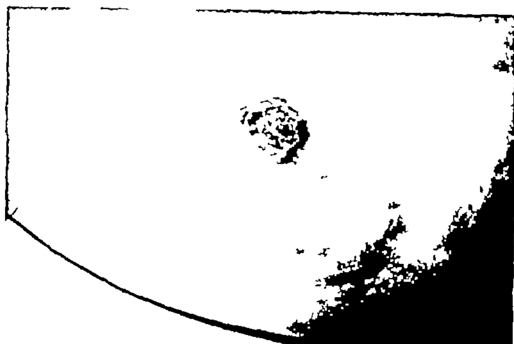




Fig 746 —Clinical photograph of early Paget's disease of the nipple There was underlying carcinoma. (W U neg 48-1456.)

Fig 747 —Photomicrograph of large Paget cells (carcinoma cells) involving the epidermis (×450) (Courtesy Dr A P Stout, New York.)

nipple. These tumors have the general characteristics of the usual carcinoma except that many are confined predominantly to the ducts (Sirtori)

Microscopically tumor fills the underlying ducts in the same fashion as intraductal carcinoma In some, carcinoma invades through the duct wall. Invariably, if enough sections are studied, a connection between the carcinoma within the duct and carcinoma in the overlying nipple can be demonstrated The large tumor cells lying within the epithelium are identical to the tumor cells lying within the ducts (Fig 747) These cells are carcinoma cells not epidermal cells (Muir) There are numerous theories concerning Paget's disease First and the majority opinion is that the tumor arises from the main ducts of the breast and secondarily involves the epidermis. Second there are two independent tumors one of the epidermis and one of the underlying ducts. This is difficult to accept, for the tumor cells of the epidermis and the underlying ducts are microscopically identical



Fig. 748 —Photomicrograph of widespread invasion of dermal lymphatics in an inflammatory carcinoma. (×140) (W U neg 49-5372.)

The tumor involving the epidermis never shows evidence of keratinization or any features of squamous or basal cell carcinoma. Third, the tumor arises in the epidermis and secondarily involves the underlying ducts. There is little evidence for this. Fourth, the tumor at times can be confined to the overlying epidermis and nipple In our experience, with possibly one exception there has been coincidental underlying carcinoma of the ducts. We have seen an instance in which epithelial mucin could be demonstrated in the Paget cells and in the underlying carcinoma. It is imperative to treat this variant of breast carcinoma by radical mastectomy

Inflammatory Carcinoma.—It is debatable whether inflammatory carcinoma represents a true pathologic entity However in its florid state certain clinical and pathologic findings can be correlated Clinically the entire involved breast is reddened and warm. On cut section cellular tumor can usually be identified through the breast parenchyma. Widespread edema of the skin is invariably present. Microscopic examination shows the dermal lymphatics packed with tumor cells (Fig 748) This finding must be present before the pathologist can confirm



Fig. 749 —Photomicrograph of papillary carcinoma without infiltration. Note layering of lining cells with loss of nuclear polarity (×180) (W U neg. 52 5317)

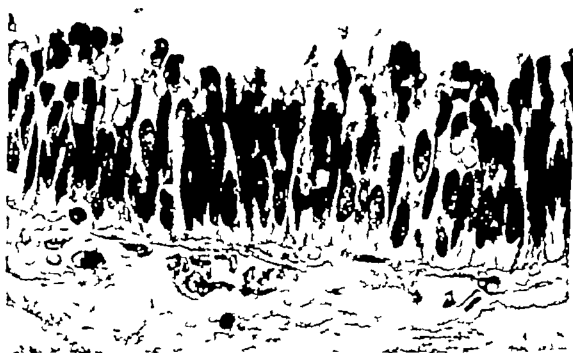


Fig 750 —Photomicrograph of papillary carcinoma demonstrating extreme layering of cells with loss of nuclear polarity (×775) (S P 55-?816.)

a clinical diagnosis of inflammatory carcinoma. These tumors are frequently quite undifferentiated.

Papillary Carcinoma.—Papillary carcinoma of the breast is a rare neoplasm in our experience. It tends to ramify within ducts and to involve an entire breast segment. Microscopically it shows papillary projections within the ducts, layering of epithelium, loss of nuclear polarity, and occasional zones of necrosis (Figs 749 and 750) Frequently these tumors are inadequately excised, recurrence may not appear for many years (five or more are not rare) Such recurrence may be local or accompanied by lymph node metastases. This is the tumor which has been often diagnosed as benign intraductal papilloma undergoing malignant change. In truth it was *malignant from the start.*

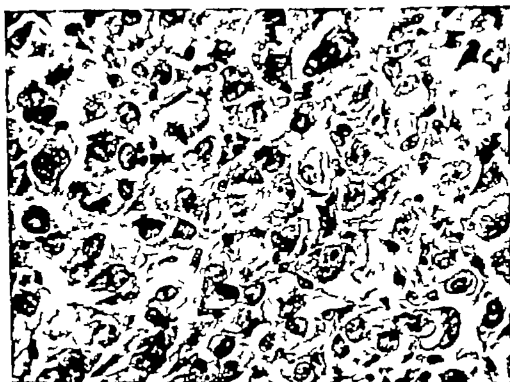


Fig 751 —Photomicrograph of an extremely undifferentiated carcinoma of the breast which contains large amounts of cytoplasmic mucin. (×400) (W U neg 50-959)

Carcinoma With Mucoid Change.—If multiple sections of the breast are stained for mucin small amounts nearly always will be found within the cytoplasm of the ductal epithelial cells. The diagnosis of mucinous carcinoma of the breast is justified only when the changes due to mucin are dominant. These tumors are often fairly well circumscribed, are palpably crepitant, and consist grossly of a currant jelly like mass often held together by delicate connective tissue septa. Hemorrhage within the mass is common. Microscopically tumor cells, often few in number are seen floating in a sea of mucin The individual cells usually form well-defined acini Apparently the patient with a tumor with these gross and *microscopic characteristics* has a fairly good prognosis By contrast if the tumor consists primarily of cells with large amounts of intracellular mucin (the rare signet ring type) the prognosis is extremely poor if not hopeless (Saphir) (Fig 751)

Epidermoid Carcinoma, Adenoid Cystic Type Carcinoma.—Epidermoid carcinoma of the breast is seldom seen. Its gross appearance differs little from the usual breast carcinoma. Excessive keratinization may be identified grossly (Fig. 752) Microscopically areas characteristic of carcinoma arising from duct epithelium are present (Stewart) Squamous metaplasia occurs irregularly throughout the breast Intercellular bridges occasionally can be identified.



Fig 752—Photomicrograph of a carcinoma of the breast with excessive squamous metaplasia. (×220) (W U neg 50-2056.)

The adenoid cystic type carcinoma is an exceedingly rare variant of breast cancer Microscopically it resembles adenoid cystic cancer of salivary gland origin. Lymph node metastases practically never occur Nayer reported a patient with this type of carcinoma who had no lymph node metastases at the time of radical mastectomy but who died thirteen years later of pulmonary metastases. We are familiar with six patients none of whom had axillary metastases none has died of tumor This disease usually has a long clinical course (Fig 753)

Acinar or Lobular Carcinoma.—Acinar or lobular carcinoma, another rare variant of carcinoma of the breast, usually occurs in younger persons. Because it is confined initially to the lobules a discrete mass may be absent. It eventually grows through the wall of the acini infiltrates the breast parenchyma, and forms a definite mass (Foote Miller) Microscopically the acini are larger than normal



Fig. 753.—Photomicrograph of well-differentiated carcinoma of the breast of the adenoid cystic type (×200.) (W U neg 52 3872.)

Fig. 754.—Photomicrograph of a lobular carcinoma of the breast. Note the lobular pattern the small cells and areas of invasion. (×200.) (W U neg 52 3452.)

and filled with closely packed cells, having few mitotic figures. Necrosis is usually absent (Fig 754) These cells probably originate from the epithelium of the terminal ducts Multiple foci of origin are apparently common. This lesion should not be diagnosed unless the microscopic characteristics of it dominate. Treatment is radical mastectomy even though the pathologist does not demonstrate growth of tumor through the duct walls. Such extension may well exist in areas not examined microscopically The prognosis is somewhat better than that of non specific breast cancer

Grading of Breast Carcinoma

Grading of breast carcinoma is believed by some to be of value in estimating prognosis (Gricouroff, Bloom) We agree that a small per cent of breast carcinomas are extremely well differentiated and confined to the ducts and that patients with medullary and papillary carcinomas have a good prognosis. Bloom uses the following three histologic factors in grading degree of structural differentiation as shown by the presence of tubular arrangement of the cells variation in size, shape, and staining of the nuclei and frequency of hyperchromatic and mitotic figures. He uses only three grades. He feels that variation in histologic pattern as shown in Fig 755 is not an argument against grading for the degree of pleomorphism and frequency of hyperchromatic and mitotic figures usually show little variation in any one tumor Follow up of his cases showed good correlation between survival and grade.

Effects of Irradiation on Carcinoma

Well planned irradiation of breast carcinoma always causes skin changes, but its effect on the tumor is unpredictable. There is no doubt that focal areas of the tumor may be sterilized, sometimes the tumor completely disappears or is replaced by fibrosis Lumb found that in tissue doses under 3,500 r complete sterilization of the breast cancer occurred in only a small number but with doses of 3,500 to 4,000 r the percentage was higher Apparent complete sterilization of breast cancer occurred only once in 13 cases receiving 3 000 to 3,500 r In the group receiving 3,500 to 4 000 r 4 of 11 were sterilized. Tumors prominently affected by irradiation contain giant cells with atypical nuclei, naked nuclei, and abnormal mitotic figures. The viability of these tumor cells is difficult to assess. In spite of large amounts of axillary irradiation, tumors commonly are found unaffected in some of the regional lymph nodes. Occasionally tumor appears to have been sterilized in one portion of a lymph node, yet unaffected in another area of the same node. Because of these findings, we are unable to objectively assess the value of irradiation to involved axillary lymph nodes (McWhirter Ackerman) We know of no clinical study which demonstrates conclusively sterilization of metastatic axillary lymph nodes by irradiation. Undoubtedly irradiation can wall off carcinoma for variable periods by partially sterilizing the tumor and by creating fibrosis. Such a palliative effect is well justified. About 30 per cent of patients receiving palliative therapy survive five years or more with full activity (Lenz)



Fig 755.—Variable microscopic patterns in a small carcinoma of the breast. Such changes illustrate the difficulty of grading some carcinomas of the breast. (×150.) (W U negs. 52 1231 52 1232 52 1233 and 52 1235.)

Effects of Steroid Hormones on the Tumor

Stilbesterol, testosterone and related compounds have been tried in different dosages for variable periods to relieve extensive inoperable carcinoma of the breast.



Fig 756.—Photomicrograph of undifferentiated carcinoma of the breast before treatment with testosterone (×400) (W U neg 50-2970)

Fig 757.—Photomicrograph of same tumor after treatment with testosterone showing prominent regression. Note naked nuclei and increased fibrosis. (×400.) (W U neg 50-2971) (Slides contributed by Dr Richard Johnson, Ellis Fischel State Cancer Hospital, Columbia, Mo)

Soft tissue lesions occurring in the older age groups are best treated by stilbesterol or other estrogenic preparations. Testosterone may cause regression of bone metastases in all age groups Of course, regression of either the primary tumor or its metastases is only temporary the majority have no objective regression at all—only

progression despite treatment Microscopically the changes produced by any steroid hormone are comparable There may be prominent collagen hyalinization increase in the amount of collagen increase in the prominence of the elastic tissue, necrosis and even complete disappearance of tumor cells The changes in tumor cells often are scattered one group of cells may disappear completely, another partially and still another be morphologically unaffected. The microscopic pattern of affected tumors does not show why there was a response to therapy There is cytoplasmic vacuolation nuclear aberrations and cell wall ruptures these changes are roughly analogous to those caused by irradiation. Rarely prominent regressive changes including complete disappearance of tumor cells have been demonstrated in both the primary lesion and axillary lymph nodes (Emerson) (Figs. 756 and 757) These morphologic changes are seen infrequently after adrenalectomy for carcinoma of the breast They are most likely to occur when adrenalectomy has been performed for inflammatory carcinoma of the breast (Eckert) We are not able to predict by histologic examination which cancer of the breast will respond to adrenalectomy

Sarcomas

Cystosarcoma Phyllodes.—The most common sarcoma of the breast is cystosarcoma phyllodes (giant intracanalicular adenofibroma) This tumor may arise from a pre-existing fibroadenoma and usually appears about ten years earlier than the average age for the onset of carcinoma These tumors are often large and produce a characteristic teardrop appearance to the breast. The nipple is flattened, but the overlying skin is unattached (Fig 758) They may be fixed to underlying fascia. Ulceration is rare cystic cleftlike spaces may be present. Infection and hemorrhage develop only if ulceration occurs Microscopically sarcomas show excessive stromal cellularity and intracanalicular invasion thus the name giant intracanalicular adenofibroma (Figs 759 and 760) The glandular or epithelial elements of this tumor practically never undergo malignant change If at operation there is any question of invasion of underlying fascia the underlying muscle should be removed and a radical mastectomy performed. It is rare for such lesions to metastasize to regional lymph nodes Treves reported one such occurrence in 77 cases It is much more common for local recurrences to appear because of inadequate excision (Lester)

Rare Sarcomas.—*Fibrosarcomas* of breast stroma usually grow to large size and form a firm often circumscribed mass. Grossly the tumors appear grayish white and usually organoid Necrosis may be present. Microscopically they have the characteristics of a fibrosarcoma (see Soft Tissues) These lesions may be distinguished clinically from carcinomas by their large size and by their failure to become attached to the skin. Although many do not metastasize to regional lymph nodes they are probably best treated by radical mastectomy

Other types of sarcomas, such as *liposarcoma* (Hill) and *hemangiosarcoma* (McClanahan) may rarely occur in the breast *Lymphangiosarcoma* occurs rarely in patients who have had long standing lymphedema after a radical mastectomy (Stewart) *Rhabdomyosarcomas* are extremely rare we have seen only one questionable case.

Lymphosarcoma —Lymphosarcoma occurs very rarely as a primary neoplasm of the breast It behaves as a primary malignant neoplasm is usually quite soft and grayish white. The *microscopic pattern is the same* as any lymphosarcoma. The regional lymph nodes are often involved the treatment of choice is radical mastectomy The prognosis often is good (Harrington)

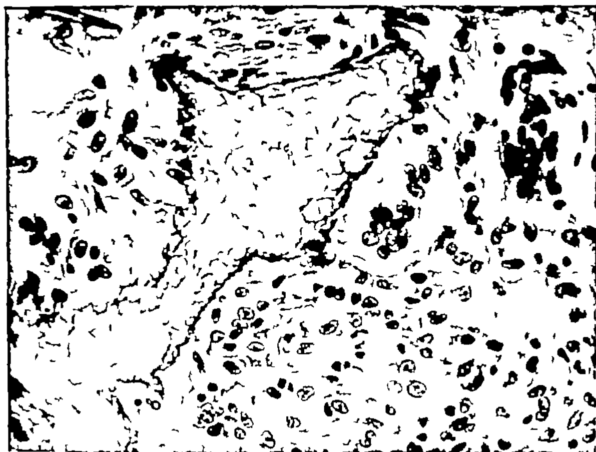


Fig 761 —Photomicrograph of foreign body giant cell reaction surrounding polyvinyl plastic (Ivalon) (×410) (AFIP 725220)

Rare Lesions

Skin lesions such as *basal cell carcinoma epidermoid carcinoma epidermal inclusion cysts* and *sweat gland tumors* may arise in the skin of the breast and should not be considered as primary breast neoplasms. *Hemangioma* and *hemangiopericytoma* may occur within the breast parenchyma. *Metastatic carcinomas* rarely affect the breast except in widely disseminated tumors such as melanomas The breast may also be affected secondarily by *lymphosarcoma* and *Hodgkin s disease*

Fungus disease (coccidioidomycosis actinomycosis) may occur with multiple sinus tract formation We have seen several instances of foreign body reaction to Ivalon This spongy plastic material is used for mamoplasty It becomes impregnated with granulation and fibrous tissue thus instead of enhancing beauty the polyvinyl plastic (Ivalon) contracts, hardens, and becomes fixed (Hollywood disease) (Hamit) Sinus tracts in the breast may also appear after the use of Ivalon (Fig 761)

CLINICOPATHOLOGIC CORRELATION

It is imperative that the clinician be skilled in accurate palpation of the breast and axilla when examining a patient with a lump in the breast. We have demonstrated that the benign or malignant nature of a dominant mass can be correctly diagnosed by *fourth year medical students in 55 per cent of instances* (5 per cent better than tossing a coin) The experienced clinician can diagnose only 70 per cent correctly Therefore, a policy of look and see must replace that of wait and see. However once lumps are exposed and sectioned the surgeon proficient in surgical pathology can grossly identify their benign or malignant nature in over 85 per cent of the cases. The fallacy of attempting to determine the presence or absence of axillary lymph node metastases by palpation is illustrated in Table 35

TABLE 35 CLINICAL IMPRESSION VS MICROSCOPIC FINDINGS

I	Clinically negative and microscopically negative	84 cases	Examiner correct in 54 per cent of cases
	Clinically negative and microscopically positive	71 cases	
II	Clinically positive and microscopically positive	124 cases	Examiner correct in 85 per cent of cases
	Clinically positive and microscopically negative	22 cases	

The error in saying that an axilla is negative when an involved node is present approaches 50 per cent Conversely the error is only about 15 per cent when the axilla is thought to contain disease because of the presence of enlarged nodes. Usually these are cases with ulceration or infection. The over all error in axillary palpation is 30 per cent. The examining physician must be well aware of certain ominous clinical findings The clinical signs indicating inoperability have been listed by Haagensen Extensive edema *of the breast obviously means that tumor* has permeated and blocked cutaneous lymphatics and is a sign of an advanced stage of the disease (Fig 762) Handley has routinely explored the second and third intercostal spaces at the time of radical mastectomy With thorough pathologic study of the axillary lymph nodes after radical mastectomy the *probability* of internal mammary lymph node metastases can be estimated. If the axillary lymph nodes are *negative* and the tumor is located in the *outer quadrants*, the internal mammary lymph nodes will practically never contain tumor If the tumor is located in the central or inner half no more than 20 per cent of the internal mammary lymph nodes will contain cancer However if the axillary lymph nodes are *positive* and the tumor arises in the outer quadrants, at least 30 per cent of internal mammary nodes will be involved if the tumor arises in *the central area* or medial half of the breast, over 50 per cent of them cc Approxi
mately a third of the patient e breast cancer w ement
of the internal mammary chain s may be extremely Haagensen
has demonstrated by routine the supraclavic operable
breast cancer that if the are involved one patients
also will have supraclavicular involvement. It y lymph
nodes are not involved the sup *n node area* The

TABLE 36. RELATIVE SIZE OF THE TUMORS WITH AND WITHOUT METASTATIC NODES—JULY 1948 TO JANUARY 1952 BARNES HOSPITAL, ST LOUIS MO

SIZE	NUMBER OF CASES WITHOUT INVOLVED LYMPH NODES	NUMBER OF CASES WITH INVOLVED LYMPH NODES	PERCENTAGE INVOLVED
2 cm or below	40	21	34 4
2 to 3 cm	31	30	49 1
3 to 4 cm.	16	23	58 9
4 to 6 cm	14	24	63 1
Over 6 cm	3	18	85 7
Total	101	116	53 0

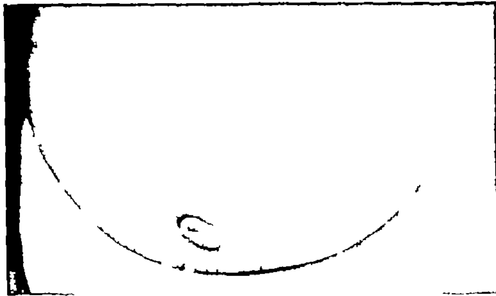


Fig. 762.—Clinical photograph of a breast in which there was rather prominent edema surrounding the nipple This is an ominous finding (W U neg 50-3770)

most important single prognostic factor after radical mastectomy is the presence or absence of involved axillary lymph nodes. The most important factor in determining whether these nodes are involved or not is the size of the primary tumor (Table 36) In estimating prognosis of breast cancer it must be remembered that in a series of patients who have not been treated 22 per cent will live five years and 7 per cent will live ten years All patients must be followed indefinitely local recurrence may occur many years after the original operation (Fig 763) All instances of supraclavicular lymph node enlargement must be proved to be cancer by biopsy Their enlargement may be only the result of a chronic inflammatory process such as tuberculosis. The presence of satellite skin nodules and parasternal nodules means that the tumor has escaped blocked lymphatics and formed subcutaneous masses. If the muscle is invaded tumor is probably in distant areas such as the anterior mediastinal lymph nodes The presence of nerve sheath and/or vessel invasion is also a sign of advanced disease and occurs almost invariably with lymph node involvement. Nerve and vessel invasion is present in about 5 per cent of cases.

Cancer of the male breast accounts for less than 1 per cent of breast cancers in both sexes. It appears to have a poor prognosis except for those patients with

CLINICOPATHOLOGIC CORRELATION

It is imperative that the clinician be skilled in accurate palpation of the breast and axilla when examining a patient with a lump in the breast. We have demonstrated that the benign or malignant nature of a dominant mass can be correctly diagnosed by fourth year medical students in 55 per cent of instances (5 per cent better than tossing a coin) The experienced clinician can diagnose only 70 per cent correctly Therefore, a policy of look and see must replace that of *wait and see*. However once lumps are exposed and sectioned, the surgeon proficient in surgical pathology can grossly identify their benign or malignant nature in over 85 per cent of the cases. The fallacy of attempting to determine the presence or absence of axillary lymph node metastases by palpation is illustrated in Table 35

TABLE 35 CLINICAL IMPRESSION VS MICROSCOPIC FINDINGS

I	Clinically negative and microscopically negative	84 cases	Examiner correct in 54 per cent of cases
	Clinically negative and microscopically positive	71 cases	
II	Clinically positive and microscopically positive	124 cases	Examiner correct in 85 per cent of cases
	Clinically positive and microscopically negative	22 cases	

The error in saying that an axilla is negative when an involved node is present approaches 50 per cent. Conversely the error is only about 15 per cent when the axilla is thought to contain disease because of the presence of enlarged nodes. Usually these are cases with ulceration or infection The over all error in axillary palpation is 30 per cent. The examining physician must be well aware of certain ominous clinical findings The clinical signs indicating inoperability have been listed by Haagensen. Extensive edema of the breast obviously means that tumor has permeated and blocked cutaneous lymphatics and is a sign of an advanced stage of the disease (Fig 762) Handley has routinely explored the second and third intercostal spaces at the time of radical mastectomy With thorough pathologic study of the axillary lymph nodes after radical mastectomy the probability of internal mammary lymph node metastases can be estimated. If the axillary lymph nodes are *negative* and the tumor is located in the outer quadrants, the internal mammary lymph nodes will practically never contain tumor If the tumor is located in the central or inner half no more than 20 per cent of the internal mammary lymph nodes will contain cancer However if the axillary lymph nodes are *positive* and the tumor arises *in the outer quadrants, at least* 30 per cent of internal mammary nodes will be involved If the tumor arises in the central area or medial half of the breast, over 50 per cent of them contain tumor Approximately a third of the patients with operable breast cancer will have involvement of the internal mammary chain These nodes may be extremely small Andreassen has demonstrated by routine exploration of the supraclavicular space in operable breast cancer that if the axillary lymph nodes are involved one third of the patients also will have supraclavicular lymph node involvement. If the axillary lymph nodes are not involved the supraclavicular lymph node area is not involved. The

TABLE 36 RELATIVE SIZE OF THE TUMORS WITH AND WITHOUT METASTATIC NODES—JULY 1948 TO JANUARY 1952 BARNES HOSPITAL ST LOUIS MO

SIZE	NUMBER OF CASES WITHOUT INVOLVED LYMPH NODES	NUMBER OF CASES WITH INVOLVED LYMPH NODES	PERCENTAGE INVOLVED
2 cm or below	40	21	34 4
2 to 3 cm.	31	30	49 1
3 to 4 cm	16	23	58 9
4 to 6 cm.	14	24	63 1
Over 6 cm.	3	18	85 7
Total	104	116	53 0

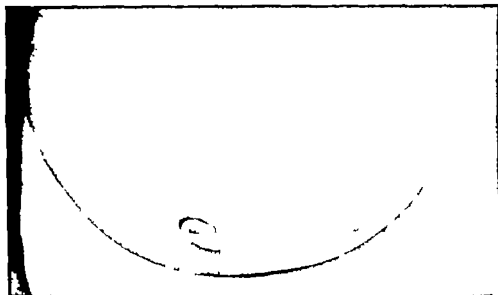


Fig. 762.—Clinical photograph of a breast in which there was rather prominent edema surrounding the nipple This is an ominous finding (W U neg 50-3770)

most important single prognostic factor after radical mastectomy is the presence or absence of involved axillary lymph nodes. The most important factor in determining whether these nodes are involved or not is the size of the primary tumor (Table 36) In estimating prognosis of breast cancer it must be remembered that in a series of patients who have not been treated 22 per cent will live five years and 7 per cent will live ten years All patients must be followed indefinitely local recurrence may occur many years after the original operation (Fig 763) All instances of supraclavicular lymph node enlargement must be proved to be cancer by biopsy Their enlargement may be only the result of a chronic inflammatory process such as tuberculosis. The presence of satellite skin nodules and parasternal nodules means that the tumor has escaped blocked lymphatics and formed subcutaneous masses. If the muscle is invaded, tumor is probably in distant areas such as the anterior mediastinal lymph nodes. The presence of nerve sheath and/or vessel invasion is also a sign of advanced disease and occurs almost invariably with lymph node involvement Nerve and vessel invasion is present in about 5 per cent of cases.

Cancer of the male breast accounts for less than 1 per cent of breast cancers in both sexes. It appears to have a poor prognosis except for those patients with

papillary carcinoma (Treves) We have little information concerning cancer of the breast in children (Hartman)

During the last decade there has been dissatisfaction with the survival of patients treated for carcinoma of the breast. Wangensteen Urban, and Handley have extended the conventional radical mastectomy McWhirter has reported a large series of patients treated by simple mastectomy and postoperative irradiation therapy In Wangensteen's group the operation included the conventional radical mastectomy combined with removal of the internal mammary chain and



Fig 763 —Clinical photograph of a patient with local recurrence of a carcinoma twenty seven years after the original operation. (W U neg 50-1781)

supraclavicular nodes There was a high operative mortality (12.5 per cent) considerable morbidity and unfortunately only 2 patients with involved internal mammary lymph nodes out of 37 survived over four years Urban's operation had practically no operative mortality little morbidity and included only the internal mammary chain with radical mastectomy It is encouraging that 8 patients out of 22 with involved mammary lymph nodes are now surviving over five years. McWhirter's results have been comparable to those reported by competent surgeons. In his group it is hard to determine what the radiation therapy contributed since no one knows as yet the effects of irradiation on involved lymph nodes. In patients carefully selected for surgery radical mastectomy still constitutes the most certain method of cure (Haagensen) In patients with disease beyond the axilla postoperative irradiation hormone therapy adrenalectomy hypo-

physectomy and at times elective oophorectomy are successful in producing palliation The natural life history of this disease makes it extremely difficult to critically analyze the end results of treatment by any method

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Chapter 19

LYMPH NODES

INTRODUCTION, BIOPSY

The microscopic interpretation of lymph node lesions is extremely difficult *probably more diagnostic errors are made on lymph nodes than in other organs.* The most common error is to incorrectly diagnose a benign node as malignant lymphoma. The reasons for these errors are many The internist requests lymph node biopsy in a patient with generalized lymphadenopathy the surgeon, tempted by its accessibility biopsies an inguinal node. Unfortunately inguinal lymph nodes invariably show chronic inflammatory changes and fibrosis which obscures the interpretation of any other pathologic process present In the presence of generalized lymphadenopathy the surgeon must biopsy the more elusive axillary or deep cervical node. Such nodes are more likely to be diagnostic than are superficial ones. A superficial cervical lymph node may show only hyperplasia, yet a deeper node of the same group shows metastatic carcinoma. Similarly the most accessible enlarged lymph node found at celiotomy may not show the pathologic process causing the intra abdominal lymphadenopathy The surgeon biopsying intra abdominal nodes or large cervical or axillary masses should have frozen section performed to be certain that the tissue is representative. This may save a second biopsy The biopsy of a lymph node in the cervical or axillary area should be

performed only by a surgeon An inexperienced physician trying to biopsy an apparently easily accessible node may be unable to find the node or encounters hemorrhage from adjacent large vessels

If there is any question that the node contains something other than a tumor an adequate sample of the biopsied lymph node must be sent directly for bacteriologic study or be placed in a sterile Petri dish in the refrigerator We recommend and follow the latter procedure, if permanent sections show an inflammatory process the material can then be taken from the refrigerator and studied bacteriologically Furthermore, the microscopic pattern of the permanent sections may be helpful in suggesting the diagnosis to the bacteriologist. In numerous instances the bacteriologic study is more rewarding than the microscopic study (Weed) The search for acid fast bacilli or fungi in the paraffin section often is fruitless

The most common reason for an incorrect diagnosis of a lymph node by biopsy is improper preparation of the material A poorly prepared slide may be produced in the following fashions carefully delay placing the node in fixative, leave it in a strong light where it will be subjected to heat and drying then incompletely fix it in some fixative such as 10 per cent formalin, run it too quickly through various solutions and have the technician cut the sections with a dull knife at about 20 or 30 micra and overstain it with hematoxylin (Figs 764 and 765) We make it our policy never to make a diagnosis on any poorly prepared lymph node that is sent to us. Moreover, we are often amazed at the confident diagnoses that others make on such sections We recommend that the lymph node be placed in some excellent fixative such as Zenker-acetic acid and thereafter carefully passed through the various solutions and be cut with a sharp knife without distortion at 5 micra. Satisfactory results can be attained with hematoxylin and eosin staining but we have been impressed by the excellent nuclear detail obtained by eosin methylene blue (Fig 766)

HYPERPLASIA

Lymph nodes respond to infection by enlarging At times such as in the large bowel or lung a primary tumor may be associated with inflammation and regional lymph node enlargement may be entirely the result of it. Regardless of the skill of the surgeon he cannot determine by palpation whether an enlarged firm lymph node does or does not contain cancer On many occasions we have been handed lymph nodes by surgeons who have told us with confidence that they were simply "checking' those nodes which they knew contained cancer If the surgeon relies on palpation he may be denying his patient a curative operation. It is not generally realized how large hyperplastic nodes may be nodes 5 to 10 cm. in diameter may be only hyperplastic. A hyperplastic lymph node may be firm and on cut section is a homogeneous gray Frozen section of such nodes are not difficult to interpret.

DERMATOPATHIA (LIPOMELANOSIS RETICULARIS OF PAUTRIER)

Dermatopathia of lymph nodes is merely advanced hyperplasia associated with chronic dermatitis. It may occur in any skin condition in which itching, scratch



Fig 764—Photomicrograph of Hodgkin's disease. The lymph node was poorly fixed and somewhat dry before being stained. No diagnosis is possible. (×600) (W U neg 51 1662.)

Fig 765—Section of the lymph node shown in Fig 764 cut with a dull knife. Note distortion. The diagnosis is difficult. (×600) (W U neg 51 1664)

Fig 766—Photomicrograph of the node shown in Figs. 764 and 765 perfectly fixed and stained. There is no cytologic distortion and the nuclear details are clear (×600) (W U neg. 51 1661)

ing and infection are prominent. The lymph node may be quite large, the cut surface bulging and the color pale yellow. Microscopically, nodal architecture is preserved. There is excessive reticulum cell hyperplasia between follicles. Large amounts of intracellular melanin pigment and macrophages containing sudanophilic material often are present (Fig. 767). These nodes may be confused with Hodgkin's disease, and if associated with monocytic leukemia would make the diagnosis extremely difficult (Laipply).



Fig. 767.—Photomicrograph of dermatopathic lymph node. Note excessive *subcapsular* reticulum cell hyperplasia. This lesion often contains melanin pigment. (Low power.) (W.U. neg. 49-4548.)

CHRONIC GRANULOMATOUS PROCESSES

The pathologist is often asked to make a definitive diagnosis of a lymph node containing chronic granulomatous inflammation. Sometimes he may make such a diagnosis with fair accuracy. However, the reaction of the lymph nodes to the presence of various bacteriologic agents as well as fungi may vary widely; in fact, some disease entities cause identical microscopic alterations. Often only careful bacteriologic study can diagnose a lymph node lesion definitively.

The surgical pathologist should know the results of prior bacteriologic studies, agglutination tests and skin tests before attempting to interpret a granulomatous lymph node lesion. The clinical history and findings may also be quite helpful.

Tuberculosis

The presence of caseation necrosis, epithelioid cells and Langhans giant cells in the cervical nodes may seem sufficient evidence of tuberculosis. These nodes

may be adherent to each other and contain large areas of necrosis (Fig. 768) With additional evidence of pulmonary tuberculosis and draining sinuses in the neck, the diagnosis becomes almost certain. However, we still do not make this diagnosis unless acid fast organisms are found, these are best demonstrated by guinea pig inoculation Staining for acid fast organisms in tissue does not often show them.



Fig 768—Gross specimen of large adherent tuberculous lymph nodes containing large zones of caseation necrosis. (W U neg 50-3030)

Tularemia

Tularemia causes caseation necrosis with less endothelioid cell production than in tuberculosis. Axillary lymph nodes may be enlarged. A history of handling or cleaning rabbits suggests that tularemia is the correct diagnosis. The organism may pass through the intact skin. In practically all cases the agglutination titer is elevated.

Brucellosis

Brucellosis causes a chronic granulomatous reaction that is indistinguishable from tuberculosis. It may even suggest Hodgkin's disease. A definite diagnosis can be made only by bacteriologic isolation of the organism together with the presence of a high agglutination titer (Weed)

Fungus Diseases

Fungus diseases cause a chronic granulomatous process which may or may not be associated with caseation necrosis. The Schiff periodic stain is extremely

helpful in outlining the capsule of organisms such as *Histoplasma capsulatum* Coccidioides and Blastomyces In some instances however the number of organisms in a given section may be so few that they are not seen by the use of this stain In such cases only bacteriologic study can be diagnostic.



Fig 769—Classic example of stellate abscess in lymphopathia venereum. (×520) (W U neg. 5? 4494) (Slide contributed by Armed Forces Institute of Pathology)

Lymphopathia Venereum

The diagnosis of lymphopathia venereum usually is possible (in the Negro) with a positive Frei test if the node involved is inguinal and the microscopic pattern is characteristic. The earliest changes in a lymph node are focal accumulations of neutrophilic leukocytes in tiny necrotic foci. These coalesce to form the classic stellate abscess (Fig 769) A marginal zone of epithelioid cells and fibroblasts appears with aging This process may become confluent and be associated with the development of cutaneous sinus tracts. In healing stages a dense fibrous wall surrounds amorphous material (Smith) This microscopic pattern is highly suggestive of the diagnosis. However we have seen it with chronic tuberculosis and Smith has reported it with chronic tularemia.

It is not rare for a lymph node containing some chronic granulomatous process to remain undiagnosed despite careful and extensive bacteriologic and pathologic study

BOECK'S SARCOID

Boeck's sarcoid used to be diagnosed microscopically with relative ease. The lymph node contained a noncaseating lesion, prominent reticular endothelial

may be adherent to each other and contain ... With additional evidence of pulmonary tul ... neck, the diagnosis becomes almost certain ... diagnosis unless acid fast organisms are fo ... guinea pig inoculation Staining for aci ... show them.

...0 and 771) After several ... ...wary of this diagnosis. Even ... ...nosis may be incorrect in one ... but at postmortem examina... ...Figs. 772 and 773) We believe

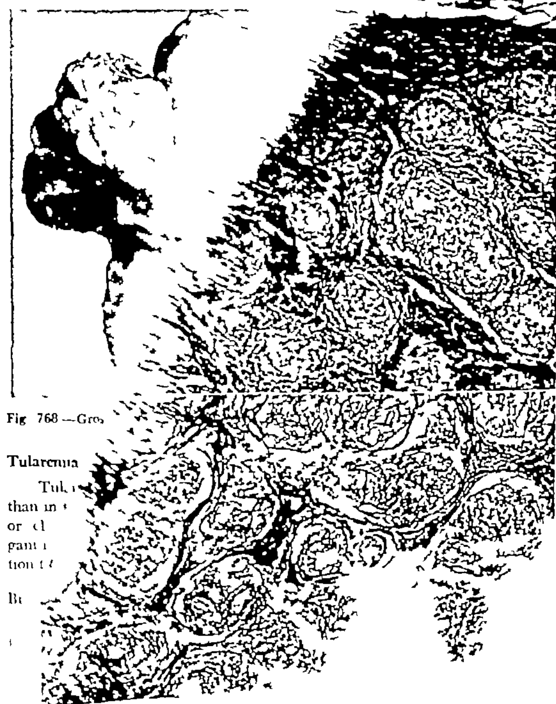


Fig 768 —Gros...

Tularemia

Tul... than in ... or cl... gani... tion t...

Bo...

Fig 770. Ph...raph of Boeck's sarcoid ... of lesions. (A...rgement) (W U neg. 49...

Fig 771 ...on of reticulin in Boeck's ... (W U neg 49-67...

that the reaction in the lymph node is a nonspecific response to a specific chemical substance The asteroid bodies and the Shaumann crystals are nonspecific (Engle) (Fig 774) We have seen lesions indistinguishable from Boeck's sarcoid

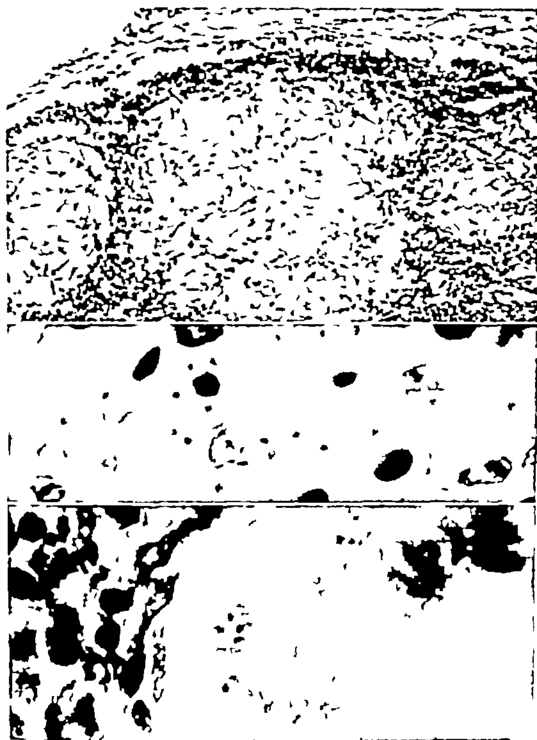


Fig 772.—Noncaseating lesion in an axillary lymph node. No organisms could be identified At postmortem examination the patient had disseminated histoplasmosis. (×200) (W U neg 50-2057)

Fig 773 —Photomicrograph of histoplasmosis. Note well-defined bodies surrounded by a clear area. (High power) (W U neg 47 394)

Fig 774 —Two prominent asteroid bodies in a sarcoidlike lesion. (×1000) (W U neg 50-707)

in lymph nodes draining a malignant neoplasm (Nadel) There was no similar lesion elsewhere We feel that Boeck's sarcoid has been used too often as a wastebasket diagnosis for numerous disease processes which have not been specifically identified.

INFECTIOUS MONONUCLEOSIS

It is rare for the pathologist to see a lymph node from a patient with infectious mononucleosis for in most instances the diagnosis is readily made by finding characteristic cells in blood smears The diagnosis is confirmed by finding an elevated heterophil antibody titer These lymph nodes are mentioned, however because they may be diagnosed incorrectly as lymphoma. The abnormal lymphocyte of this disease has been described by Custer as follows

> When stained lightly with hematoxylin and eosin in thin sections, it varies from 12 to 15 microns in diameter occasionally larger and is round except when distorted by crowding The cytoplasm is homogeneous and faintly acidophilic. The centrally or eccentrically placed nucleus is sharply delineated by a thin membrane which blends with the marginal chromatin particles chromatin is irregularly distributed to lend a mottled appearance and it occasionally forms angulated bars. Indentation and folding of the nuclei can be demonstrated in relatively few cells. It is virtually impossible to determine in the sectioned material whether a true nucleolus is present or not, nor could fenestration be evaluated. We regard these cells as atypical or abnormal lymphocytes closely related to if not identical with those found in the peripheral blood.

Lymph node reaction varies from a predominant follicular hyperplasia to a pattern suggesting a lymphoma because of reticuloendothelial and lymphocytic proliferation in the medullary cords (Custer) (Fig 775)

MALIGNANT LYMPHOMA

The microscopic diagnosis of malignant lymphoma may be extremely difficult there is no doubt that the diagnosis often is made upon benign lymph nodes. We have seen an incorrect diagnosis of lymphoma made in excessive nodal hyperplasia, in a lymph node reacting to tick bite (Allen), in one draining a vaccination site, and even in cat scratch disease. Cat scratch disease probably caused by a virus demonstrates characteristic lesions in lymph nodes consisting of multiple abscesses with necrotic centers surrounded by a zone of epithelioid cells and scattered giant cells (Winship Daniels) We have seen generalized lymphadenopathy at times associated with splenic and liver enlargement produced by anticonvulsant drugs such as Mesantoin and Peganone Microscopically the lymph nodes show excessive reticulum cell hyperplasia eosinophilia, but no Reed-Sternberg cells (Saltzstein) (Fig 776) The lymph node of Letterer-Siwe's disease may be confused with a lymphoma because of the diffuse reticuloendothelial hyperplasia and the large number of eosinophils (Fig 777) The excessive hyperplasia of lymph nodes associated with rheumatoid arthritis may be erroneously diagnosed as Hodgkin's disease or giant follicle lymphoma (Motulsky) Once the diagnosis of a malignant

lymphoma, such as Hodgkin's disease is made, the patient's prognosis becomes hopeless. Irradiation and perhaps nitrogen mustard may be given. If an incorrect diagnosis has been made, the use of these agents is dangerous. We have seen one instance where a diagnosis of lymphosarcoma was made and later proved incorrect. The patient was irradiated excessively and died from the effects.

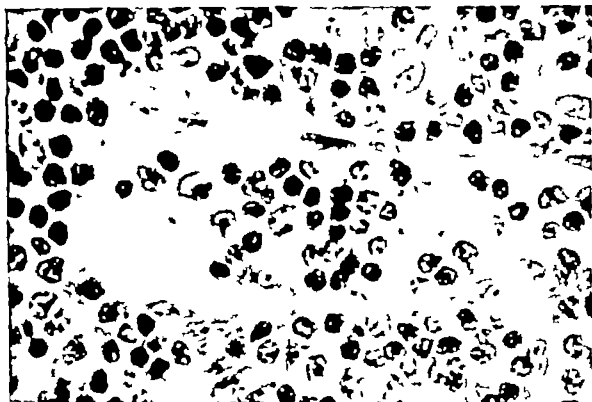


Fig 775.—Photomicrograph of a lymph node showing a medullary cord containing hyperplastic lymphocytes, reticulum cells, and lining endothelium of a sinus. The sinus contains normal and atypical lymphocytes. One of the latter lying outside of the sinus is in the upper center (×1000.) (AFIP 94401.) (From Custer, R. P., and Smith, E. B.: Blood 3: 830, 1948.)

A less common error is illustrated by another patient who had a diagnosis of hyperplasia made on an excised cervical lymph node. After being free of symptoms for ten years, the patient felt an abdominal mass. Exploration showed extensive lymphosarcoma. He died of disseminated disease the same year despite treatment. Review of the biopsy made ten years before showed giant follicle lymphoma.

Custer has presented many interrelationships between the various types of lymphoma. We are not yet willing to accept all of these but do agree that giant follicle lymphoma shades into lymphosarcoma and can have a blood picture indistinguishable from lymphocytic leukemia. Also the undifferentiated form of Hodgkin's disease, Hodgkin's sarcoma, is closely related to undifferentiated reticulum cell sarcoma. Monocytic leukemia is closely related to diffuse reticulum cell sarcoma. However, we have not yet seen transition from giant follicle lymphoma to Hodgkin's disease as reported by Custer. Follicular forms of Hodgkin's disease exist (Rappaport).

Fig 776.—Photomicrograph of a lymph node with profound reticulum cell hyperplasia, eosinophilia, and nuclear debris. The patient was a child with generalized lymphadenopathy and splenomegaly and had been taking Peganone an anticonvulsant drug. Clinically and pathologically he was first considered to have malignant lymphoma. With discontinuance of the drug symptoms and clinical findings completely disappeared and the child was well. (×750.) (W U neg 58-1456.)

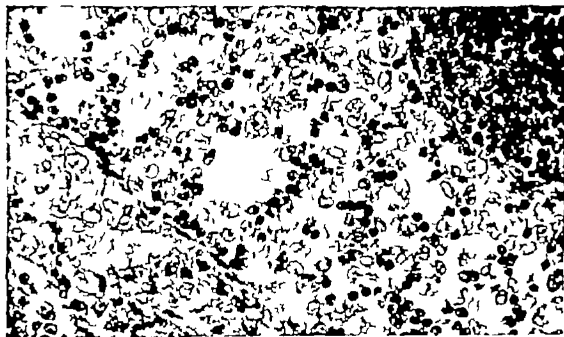


Fig 777.—Diffuse reticulum cell hyperplasia and eosinophilia in a patient with Letterer Siwe disease. (×460.) (W U neg 50-475.) (Slide contributed by Dr A. R. Crane, Philadelphia, Pa.)

The diagnosis of *giant follicle lymphoma* involving lymph nodes is difficult to make. Patients with this disease may be in good physical condition they have generalized lymphadenopathy and commonly a palpable spleen Grossly the sectioned node may show follicles as small gray areas. The differential diagnosis includes reactive follicular hyperplasia and giant follicle lymphoma The differential diagnosis is well demonstrated by Rappaport s table (Table 37)

TABLE 37 ARCHITECTURAL AND CYTOLOGICAL FEATURES THAT FAVOR A DIAGNOSIS OF FOLLICULAR LYMPHOMA OR REACTIVE FOLLICULAR HYPERPLASIA, RESPECTIVELY*

FOLLICULAR LYMPHOMA	REACTIVE FOLLICULAR HYPERPLASIA
Architectural Features	
1 Complete effacement of normal architecture	1 Preservation of nodal architecture
2 Even distribution of "follicles" throughout cortex and medulla	2 Follicles more prominent in the cortical portion of lymph node
3 Slight or moderate variations in the size and shape of the "follicles"	3 Marked variations in size and shape of follicles with presence of elongated angulated and dumbbell-shaped forms
4 Fading of "follicles"	4 Sharply demarcated reaction centers
5 Massive infiltration of capsule and pericapsular fat with or without formation of neoplastic follicles outside the capsule	5 No or only moderate infiltration of capsule and pericapsular fat tissue with inflammatory cells that may be arranged in perivascular focal aggregates (when associated with lymphadenitis)
6. Condensation of reticulin fibers at periphery of "follicles"	6 Little or no alteration of the reticular framework
Cytological Features	
1 "Follicles" composed of neoplastic cells exhibiting cellular pleomorphism with nuclear irregularities	1 Centers of follicles (reaction centers) composed of reticulum cells and their histiocytic derivatives with few or no cellular and nuclear irregularities
2. Lack of phagocytosis	2 Active phagocytosis in reaction centers
3 Relative paucity of mitotic figures usually without significant difference in their number inside and outside the "follicles" occurrence of atypical mitoses	3 Moderate to pronounced mitotic activity in reaction centers rare or no mitoses outside reaction centers no atypical mitoses
4 Similarity of cell type inside and outside the "follicles"	4 Infiltration of tissue between reaction centers with inflammatory cells (when associated with lymphadenitis)

*From Rappaport H Winter W J and Hicks E B Cancer 9: 792 1956

Certain features are of little help in differentiating follicular lymphoma and reactive follicular hyperplasia numerical increase in follicles dimensional increase in follicles, compression of sinuses cracking phenomena packing of lymphocytes around follicles, and fusion of follicles (Rappaport)

In syphilis there may be prominent hyperplasia of the germinal centers and at times prominent granulomatous changes (Evans) It is useful to separate giant follicle lymphoma from other lymphomas because it often has a long clinical course and responds dramatically to small amounts of irradiation therapy (Meyer) (Figs. 778 and 779) However all these cases eventually progress to lymphosarcoma or lymphocytic leukemia (Baehr) The notched nucleus cell" has been seen rather frequently in the peripheral blood of patients with follicular lymphoma (Figs 780 and 781)

Lymphosarcoma of the lymph nodes can be divided into a small-cell variety and a large-cell variety often designated as reticulum cell sarcoma (Figs. 782 and



Fig 778 – Even distribution of follicles in cortex and medulla in giant follicle lymphoma. (Low power) (W U neg 48-5750)

Fig. 779 —Detailed view of a single enlarged follicle in giant follicle lymphoma. There was no phagocytosis. (Moderate enlargement.) (W U n 48-5746.)

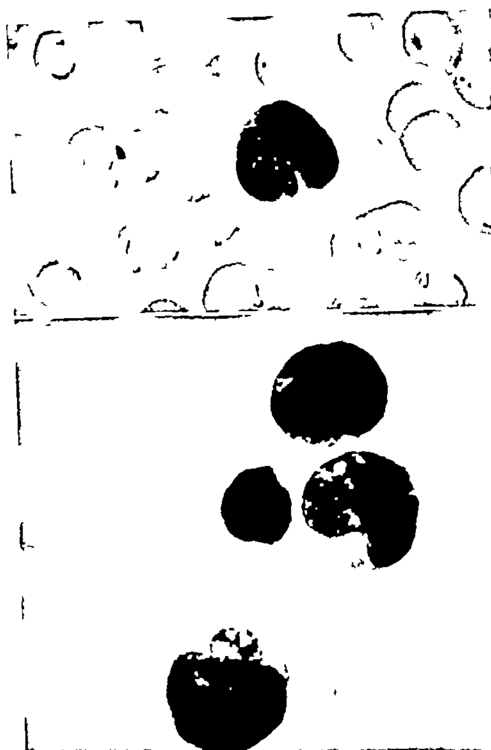


Fig 780.—Blood smear from a patient with mixed type follicular malignant lymphoma so-called "notched nucleus cell." (Wright stain.) (×1080.) (AFIP 509576.)

Fig 781.—Blood smear from same patient as in Fig 780. Abnormal lymphocytes interpreted as neoplastic in smear (lymphosarcoma cells). (Wright stain.) (×1080.)

(From Rappaport, H, Winter, W. J., and Hicks, E. B.: Cancer 9: 792, 1956.)

783) The frequency of reticulum cell sarcoma and lymphosarcoma of the small cell type varies according to the criteria of the individual pathologist. If Oberling and Warren's criteria are used for reticulum cell sarcoma, the diagnosis is made only when the lymph node is replaced by large cells with prominent nuclei, prominent nucleoli, and pink cytoplasm. The reticulin stain is of no value diagnostically

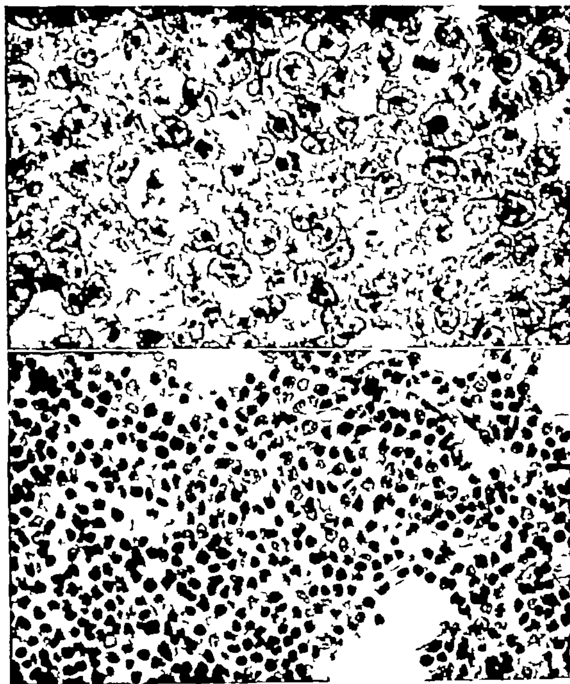


Fig 782 —Detailed iculum cell sarc g an inguinal lymph node. As may rarely occur p as present. I or cells have well-defined nuclei prominent nucleoli nt cytoplasm. U neg 52

Fig 783 —Lymphos small cell t nnodal fa not differentiate this tumor fr ukemia. (× neg. 49-6

The lymphosarcoma of the small-cell type completely or partially replaces normal lymph node structures and extends at times into perinodal tissues. We have not found it possible to distinguish between the lymph node of lymphosarcoma of the small cell type and the lymph node of chronic lymphocytic leukemia Grossly the nodes of lymphosarcoma may form large masses, but the individual nodes are not ad herent. They appear highly cellular and occasionally contain areas of necrosis (Fig 784) The clinical history the blood count, and the bone marrow findings are required to differentiate chronic lymphocytic leukemia from the small-cell type lymphosarcoma



Fig 784 —Gross photograph of a mass of nodes in lymphosarcoma. Note separation of the lymph nodes and occasional areas of necrosis. (W U neg 49 3387)

Hodgkin s disease involving the lymph nodes may be difficult to interpret. We believe that Hodgkin s disease is incurable although life may be prolonged by irradiation therapy (Peters) There is great variation in the evolution of this disease. Grossly the nodes become adherent to one another and on cross section show fibrotic, necrotic, and cellular areas. Microscopically there are a large num ber of Reed-Sternberg cells, obliteration of normal node architecture, areas of fibrosis, and eosinophils. The key to the diagnosis we believe is the identification of the Reed-Sternberg cells which originate in the reticuloendothelial system have prominent nuclei, and very prominent nucleoli (Fig 785) In the absence of Reed-Sternberg cells the diagnosis of Hodgkin s disease is not justified. Reed Sternberg cells have been confused with megakaryocytes, but the latter contain an intracytoplasmic substance that gives a strongly positive reaction when stained by the periodic acid Schiff method (Fisher) Fibrosis, eosinophils, and necrosis

support the diagnosis of Hodgkin's disease but in themselves are not diagnostic. The breakdown of Hodgkin's disease into various types such as Hodgkin's paragranuloma, Hodgkin's granuloma and Hodgkin's sarcoma is not warranted because each type blends with the others and all types may be seen in a single group of lymph nodes. However, the cases identified as Hodgkin's sarcoma do poorly as a group. There are a few cases of Hodgkin's disease which have a long clinical duration (Harrison, Bonenfant).

A cellular study of lymph node imprints is helpful in correlating the findings of the hematologist with the morphologic structure of the node seen by the pathologist (Moore). For instance, in one patient the imprint demonstrated the correct diagnosis to be myelocytic leukemia although the tissue section was diagnosed as lymphosarcoma. We believe that the study of lymph node imprints should be used as a routine procedure, particularly in the diagnosis of lymphomas.

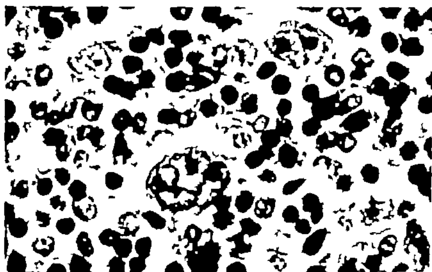


Fig. 785.—Photomicrograph of classic Reed-Sternberg cells with multilobated nuclei, and prominent nucleoli. (High power.) (W. U. neg. 48-4608.)

CLINICOPATHOLOGIC CORRELATION

The clinicopathologic difference between Hodgkin's disease and lymphosarcoma is shown in Table 38 (Ackerman). Nitrogen mustard can cause profound alteration in the lymph nodes of Hodgkin's disease. Areas of destruction occur with focal necrosis and nuclear aberrations (Figs. 786 and 787). However nitrogen mustard cannot completely sterilize a lymph node while radiotherapy can. The primary treatment in practically all of these lesions is irradiation therapy. Infrequently lymphosarcoma may be a localized process in the skin, soft tissue, gastrointestinal tract, or lung and in such areas be resectable and curable. But when the patient is first seen, the process usually is already disseminated, and irradiation is only palliative. Hodgkin's disease is primarily a radiotherapeutic problem and in our experience is not curable by operation. As noted previously irradiation therapy will prolong the life of the patient with Hodgkin's disease (Peters). It seems certain that irradiation will prolong *useful* life in leukemia

although probably does not prolong its duration Giant follicle lymphoma often has a long biologic course and is alleviated by small amounts of irradiation therapy

TABLE 38 CLINICAL DIFFERENCES BETWEEN LYMPHOSARCOMA AND HODGKIN'S DISEASE*

	LYMPHOSARCOMA	HODGKIN'S
Age	Common in the very young and old	Peak between 18 and 38 rare at puberty
General condition of patient (early stages)	Often affected	Usually excellent
Pruritus	Usually not present	May precede and fairly frequently accompanies
Fever	Very rarely observed in early cases	May be found in early cases
Presence of a lesion in the upper air passages or in the gastrointestinal tract	Strong suggestion of primary lymphosarcoma of these structures	Rarely involves these structures
Lymph node involvement	Often symmetrical	Often unilateral
Cervical lymph nodes	Often bilateral upper cervical, spinal and jugular chains	Often unilateral lower cervical jugular chain
Physical character	Often voluminous ovoid mass	Often polylobated
Sternal lymph nodes (Goldman 1945)	Practically never involved	When involved probably Hodgkin's
Epitrochlear lymph nodes	May be involved	Practically never involved
Basal metabolic rate (afebrile cases)	May be elevated	Invariably normal
Response to radiations	*Great radiosensitivity* Immediate response	Marked radiosensitivity delayed response

*Ackerman, L. V., and del Regato J A. Cancer Diagnosis, Treatment, Prognosis, St. Louis, 1947 The C V Mosby Co., p 1050

METASTATIC TUMORS

Lymph nodes are frequently found to contain unexpected malignant processes. We are often asked to decide whether this process is an epithelial or a mesodermal tumor and also the probable site of origin In some instances the microscopic changes are sufficiently diagnostic to give this information, but in others the changes warrant only a shrewd guess. A small firm right supraclavicular lymph node may contain well-differentiated papillary tumor Tumors with this pattern forming acini *and having* psammoma bodies do not originate within the oral cavity Such tumors could arise from the thyroid, however if no other nodes are involved in the thyroid area, this would be unlikely Such a papillary tumor would be unusual from the breast or lung although the location of the metastases would be compatible with such origin. The most likely source of the primary tumor might well be the ovary (Fig 788) There are many cases however in which all the pathologist can say is that the lymph node is replaced by a highly undifferentiated malignant tumor source unknown In some instances *biopsy of a peripheral* lymph node may obviate a major surgical procedure. A small supraclavicular node may be biopsied and found to contain carcinoma metastatic from the breast in such cases an operation is fruitless. When well-differentiated squamous car

cinoma replaces a lymph node central necrosis may make the node cystic. We have seen such lesions diagnosed clinically as benign cysts (Fig 789) Carcinoma may be so undifferentiated that it cannot be distinguished from lymphosarcoma.

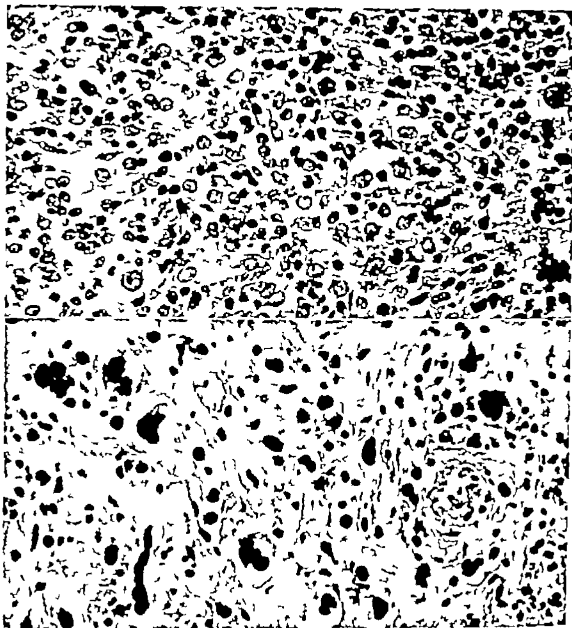


Fig 786.—Photomicrograph of typical Hodgkin's disease Note pleomorphism with reticuloendothelial proliferation and numerous Reed-Sternberg cells. (×480) (W U neg 50-5996)

Fig 787.—The patient had a transient response to nitrogen mustard and died. This lymph node shows fibrosis and prominent nuclear abnormalities There had been no irradiation therapy (×480) (W U neg 50-5994)

Under these circumstances the reticulin stain and the cytologic details are not helpful. The pattern of tumor cells growing in small nests separated by stroma is often the *only* diagnostic feature of a carcinoma (Figs 790 and 791)



Fig 788.—Metastatic carcinoma in a lymph node. Tumor is epithelial with a papillary arrangement. Primary neoplasm arose from the ovary (×300) (W U neg 52-4089)

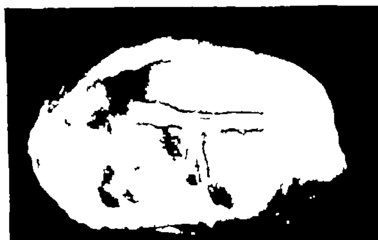


Fig 789—Gross photograph of cystic degeneration of a cervical lymph node replaced by well-differentiated squamous carcinoma. (W U neg 50-2118)

RARE LESIONS

Whipple's disease an extremely rare entity is characterized by deposits of fat and fatty acid in the intestine and mesenteric lymph vessels. Clinically there is gradual weight loss weakness steatorrhea indefinite abdominal symptoms, and

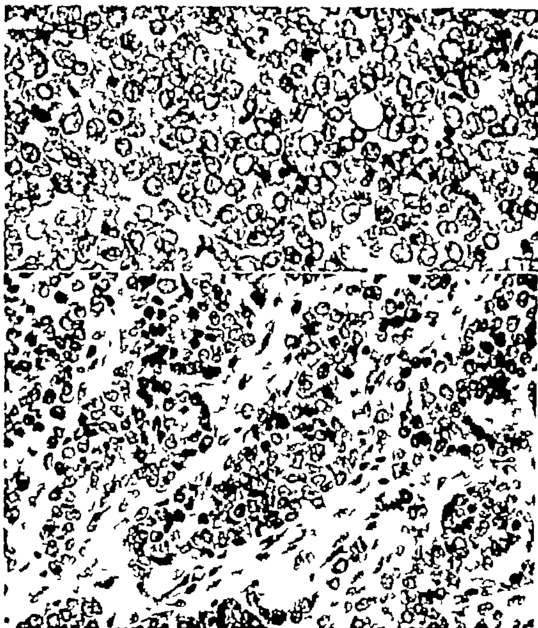


Fig 790.—Area in a lymph node of replacement by carcinoma which is impossible to differentiate from lymphosarcoma. (×420) (W U neg 51-4668.)

Fig 791—Photomicrograph of another lymph node from the same case referred to in Fig 790 in which the diagnosis of carcinoma can now be made because of the carcinoma cells growing in small nests. (×300) (W U neg 51-4669)

polyarthritis. It has been shown by Puite that peripheral node biopsy may establish the diagnosis PAS-positive material is found within the macrophages of the lymph node (probably a glycoprotein) (Black-Schaffer) This material was

abundant in the two cases we have seen The cytoplasmic vacuoles had characteristic sickle form particles (Sieracki)

Disseminated lupus erythematosus may be rarely diagnosed by lymph node biopsy (Fig 792) In such nodes there is a peculiar form of necrosis associated with hematoxylin bodies which have been found histochemically to be aggregates of smudged lymphocytes (Klemperer)

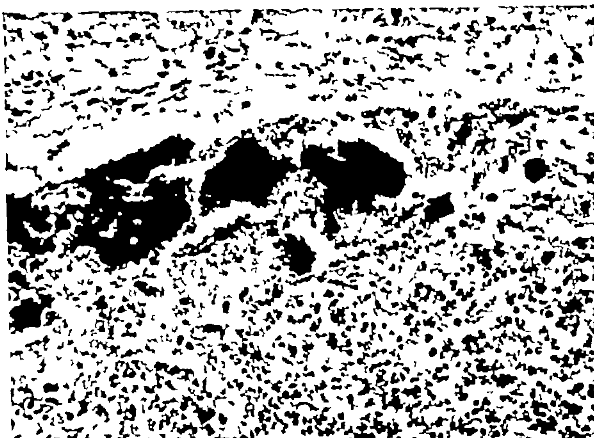


Fig 792 —Photomicrograph of lymph node with hematoxylin bodies in a patient with disseminated lupus erythematosis. The diagnosis of this disease was made on the basis of the pathologic alterations in the lymph node (×260) (W U neg 55 3684)

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Chapter 20

SPLEEN

INTRODUCTION

The functions of the spleen and their relation to morphology are mysterious and poorly understood. The surgical pathologist often is frustrated by the lack of pathologic alterations of diagnostic value. The spleen is removed from patients with diverse clinical syndromes. If the pathologist does not know the clinical and laboratory data, particularly the hematologic findings, he will be unable to make a pathologic diagnosis. Tabulation of positive pathologic changes from numerous articles and textbooks aid very little. We have tried unsuccessfully to chart the significant pathologic changes seen in each clinical syndrome. Only the changes which appear to be most significant are mentioned. These changes frequently are not diagnostic.

BIOPSY

In the United States biopsy of the spleen is not done as a rule mostly because of the technical difficulty at operation and the fear of hemorrhage after needle biopsy Certainly splenic puncture should not be performed upon patients with bleeding tendency The risk of this diagnostic procedure has been grossly exaggerated for instance Moeschlin did 300 punctures of the spleen without mortality and essentially without morbidity The method proposed by Block (splenic puncture using the Vim-Silverman needle) would seem the most effective. Tissue so obtained may be fixed, cut, and stained as a conventional section Block and Ferris reported a large number of splenic punctures in which a definitive diagnosis was made which could not be resolved by bone marrow biopsy lymph node biopsy and clinical data. At the time of operation for some obscure process the surgeon may be confronted with a large liver and spleen The liver is usually biopsied, but the spleen is sacrosanct because of the supposed danger of hemorrhage and inherent technical difficulties. However biopsying both organs can produce a diagnosis which may not be made by liver biopsy alone.

DYSSPLENISM (HYPERSPLENISM)

The concept of pathologic physiology of the spleen formulated by Doan is termed hypersplenism. This concept is a comforting and understandable one for the pathologist The name suggests overactivity, but as Moore has indicated a better name might be *dyssplenism* These changes may be selective affecting one or all combinations of the blood elements Reduction in polymorphonuclear leukocytes is called *neutropenia* reduction in all blood elements is *splenic pancytopenia* If hemolysis is prominent the designation is *acquired hemolytic anemia* a decrease in platelets is called *thrombocytopenic purpura* Dyssplenism secondary to chronic leukemia or malignant lymphoma may occur Splenectomy is particularly helpful in the patients with chronic lymphocytic leukemia (Reinhard)

Harrington has demonstrated that if small amounts of blood from a patient with thrombocytopenic purpura are given to a normal person a substance as yet unidentified will cause a precipitous fall in platelets. If a patient has thrombocytopenic purpura and the bone marrow study is normal, then removal of the spleen is frequently highly beneficial If the bone marrow is not forming platelets splenectomy will not be helpful Furthermore in thrombocytopenic purpura Harrington (1956) has demonstrated that when patients develop antibodies to their own platelets splenectomy will be successful (68 out of 83) However if they do not form such antibodies splenectomy is usually not successful (5 out of 21)

The changes found in the spleen of idiopathic thrombocytopenic purpura have been summarized by Bowman as follows slight to moderate enlargement of the spleen an increase in the number of moderately dilated sinusoids marked increase in the number of germinal centers persistence of normal marginal zones of large lymphocytes about many follicles a nonspecific increase in megakaryocytes, and a normal number of eosinophils and neutrophils in the red pulp This condition is one of the main indications for splenectomy (Coller)

Acquired hemolytic anemia cannot be discussed without mentioning congenital hemolytic anemia. In congenital hemolytic anemia there is a hereditary hemolytic tendency The red blood cells are abnormal (spherocytes) They are thicker than normal red blood cells and become trapped in the interstices of the spleen. If washed normal red blood cells are given a patient with congenital hemolytic anemia the cells survive normally Conversely if abnormal spherocytes are given a patient without congenital hemolytic anemia their survival remains short supporting the concept that the erythrocyte is defective. Furthermore this defect persists after removal of the spleen About one half of the cases of acquired hemolytic anemia have some other significant pathologic abnormality In fact almost any disease accompanied by an enlarged spleen can be associated with this phenomenon We have seen acquired hemolytic anemia in various forms of leukemia, Hodgkin's disease, Boeck's sarcoid, tuberculosis and brucellosis. The Coombs test is used to distinguish between the acquired and congenital types of hemolytic anemia. The patient's washed red cells are mixed with antihuman globulin rabbit serum the test is positive with agglutination. Young called this type of anemia chronic hemolytic disease with erythrocyte bound antibody In about half the instances the acquired hemolytic anemia occurs without a com

plicating pathologic abnormality Splenectomy may or may not be helpful in the acquired type. The pathologic changes in congenital and acquired types are quite similar The spleen is enlarged (100 to 1 000 grams) fairly firm, deep red, has a thin capsule, and no grossly discernible malpighian follicles. Microscopically there are remarkably few changes. Germinal centers usually are present. The inter sinusoidal cords are congested with empty spaces between them. The endothelial cells lining the sinuses are prominent. Blood pigment and erythropoiesis are present in congenital hemolytic anemia (Wiland)

Myeloid metaplasia

> Myeloid metaplasia is a clinical and pathologic syndrome of varied cause which is characterized by the constant occurrence of extramedullary hematopoiesis in the spleen and almost always in the liver splenomegaly and usually hepatomegaly, and an anemia with immature red and white cells in the peripheral blood (Block)

In this rare poorly understood condition myelofibrosis of the bone marrow exists, at times associated with myelosclerosis. The extramedullary hematopoiesis present in the spleen liver lymph nodes, and other organs is considered by some to be a compensatory mechanism It would therefore not seem logical ever to remove the spleen for this condition The relation of this lesion to leukemia is still debated. Some observers believe there is no relation (Loeb) while others believe that it is merely a leukemia difficult to diagnose because of the myelofibrosis and the myelosclerosis (Heller) This condition can be diagnosed when there is myelofibrosis evidence of extramedullary hematopoiesis, and immature cells in the peripheral blood. Transfusions are usually used to combat the anemia a significant degree of hemosiderosis may develop In some instances the anemia is *resistant because of associated hemolytic phenomena. Such changes* have been interpreted as dyssplenism (Moore) and splenectomy has been performed as a lifesaving procedure These spleens are extremely large (1 000 to 2 000 grams) brick red to brownish red, and partially fibrotic. Microscopically there is con gestion, small and diluted follicles, and hemosiderosis, and most important, all bone marrow elements are present. Large numbers of megakaryocytes and erythroid cells are prominent (Figs. 793 795) Biopsy of the liver in these cases shows extreme extramedullary hematopoiesis. Splenectomy has proved of value in some cases Several patients have regained normal activity with absence of hemolytic phenomena and anemia The longest any patient has been followed is about five years

TABLE 39 SPLENECTOMIES PERFORMED AT BARNES HOSPITAL, 1947 1956

CONDITION	NO OF PATIENTS	PER CENT IMPROVED
Idiopathic thrombocytopenic purpura	64	80
Acquired hemolytic anemia	19	80
Hereditary spherocytosis	15	100
Chronic lymphocytic leukemia	20	60
Lymphoma	17	50
Hypoplastic anemia	11	40
Myeloid metaplasia	7	50
Miscellaneous	31	60
Total splenectomies	184	

ACTH cortisone and other steroids are now used to treat effectively many cases of idiopathic thrombocytopenic purpura and acquired hemolytic anemia (Loeb)

Table 39 indicates the conditions for which splenectomy is done and the results.



Fig 793 —Gross photograph of a huge spleen (3200 grams) in a patient with extreme myelosclerosis and myelofibrosis, with subsequent anemia and failure to respond to all therapeutic measures. Nodule represents zone of extreme extramedullary hematopoiesis. (W U neg 52 3980)

CONGESTIVE SPLENOMEGALY (SO CALLED BANTI'S SYNDROME)

Congestive splenomegaly is a better term than Banti's disease which is not a disease but a syndrome (Larrabee) In congestive splenomegaly there are enlargement of the spleen an anemia leukopenia thrombocytopenia, and often alarming gastric hemorrhages secondary to a collateral circulation which develops between the portal and peripheral venous systems. This condition develops in the presence of increased pressure in the portal circulation as reflected through the splenic vein The etiology can be extra or intrahepatic. If intrahepatic, it is usually the Laennec type but other types of cirrhosis can also cause it. In the extrahepatic type there may be stenosis sclerosis or cavernous transformation of the portal circulation or thrombosis of the splenic vein. At times no factor can be identified. The portal circulation has no valves and carries about three fourths of the circulation of the liver and the hepatic artery carrying oxygen supplies the other one fourth. Both of these vessels have a common exit channel the hepatic vein, which empties into the inferior vena cava. According to Herrick, in



Fig 794.—Extreme myelofibrosis and myelosclerosis in the patient referred to in Fig 793. (×200) (W U neg 52-4493)

Fig. 795.—Extensive extramedullary hematopoiesis was found at postmortem examination. It involved practically every organ in the body including such tissues as the epididymis, the retroperitoneal soft tissues the adrenal, etc. This section shows large clusters of megakaryocytes within a lymph node. (×400) (W U neg 52-4492.)

Fig 796 —Photomicrograph of congestive splenomegaly with increased fibrosis and prominent vascular channels lined by endothelial cells. (High power) (W U neg 48-5171)





Fig 797 —Roentgenogram of a large cyst of the spleen. (W U neg 50-3794)

Fig 798 —Gross specimen of this partially calcified cyst lined by stratified squamous epithelium. (W U neg 50-3542)

a normal liver portal pressure rises 1 mm. for every 40 mm. of arterial pressure, and in the cirrhotic liver it rises 1 mm. for every 6 mm. of arterial pressure. Mc Indoe could not confirm these findings. He demonstrated the important fact that in advanced cirrhosis if fluid was perfused through the portal circulation all but 13 per cent escaped through the collateral circulation. Because of this, increasing responsibility is thrown onto the hepatic artery And when this fails, hepatic insufficiency occurs. With such changes there is naturally prominent





Fig 799.—Gross photograph of a well-delimited and apparently primary lymphosarcoma of the spleen, weighing 470 grams. The patient, a 66-year-old woman, later developed disseminated disease. (W U neg 54 3654)

Fig 800.—Gross photograph of Hodgkin's disease involving the spleen, weighing 800 grams. The patient, a 76-year-old man, had no other clinical or pathologic evidence of this disease. The patient presented extreme pruritus, which disappeared after removal of the spleen. (W U neg 57 7039)

increase of portal pressure which leads to long-continued congestion of the spleen The spleen enlarges anemia develops, and collateral circulation becomes prominent With still further time the spleen becomes firmer with increased fibrous tissue and section through such removed spleen shows prominent vascular channels lined by well-defined endothelial cells (Fig 796) These same changes can occur in the spleen with thrombosis of the portal vein or a main tributary The thrombosis may be the result of inflammation trauma, or extrinsic pressure by

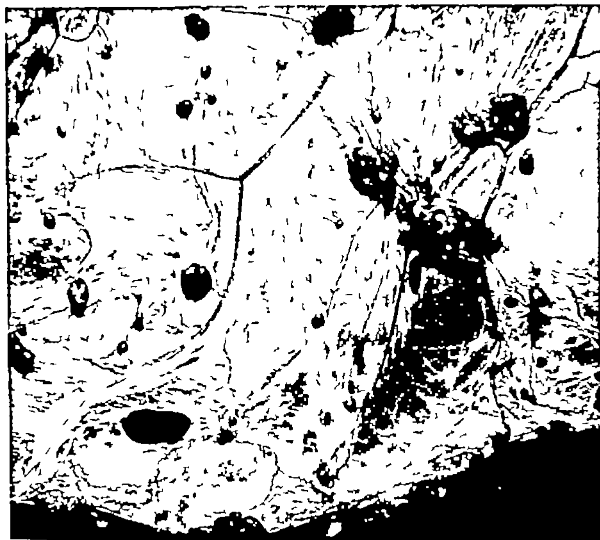


Fig 801 —Splenosis in small nodules on the peritoneal surface. This patient previously had a ruptured spleen. (W U neg 55 3599)

inflammatory or neoplastic tissue (Whipple) The obliterative fibrotic process that takes place at birth in the umbilical vein and ductus venosus as they empty into the left portal vein can also occur as a further extension into the main portal vein and this type of lesion although rare, may be seen in young children. Cavernous transformation of the portal system or its main tributaries is a condition of unknown etiology which can also cause such alterations. Splenectomy without shunt is successful when the coronary vein joins the portal system proximal to the point of obstruction otherwise shunt is indicated (Rousselot) Various types

have been done, including anastomosis of the splenic vein to the renal vein and anastomosis of the portal vein to the vena cava (Blakemore) The results from these operations have been encouraging

TUMORS

Primary tumors of the spleen are rare. Traumatic cysts can occur and we have seen large cysts lined by squamous epithelium (Montgomery) (Fowler) (Figs. 797 and 798) Of the primary malignant tumors lymphosarcoma is the most common (Figs. 799 and 800) Angiosarcoma and hemangioma can also occur (Pines) Needless to say the only curative treatment is surgical (Gordon Bostick) Secondary carcinoma of the spleen is uncommon With a disseminated malignant tumor such as malignant melanoma, it may be involved and it is implicated in widely disseminating breast cancer Upon occasion we have seen practically every type of tumor with widespread metastases involve the spleen. Herbut reported 23 cases with secondary involvement of this organ

RARE LESIONS

Congenital absence of the spleen may be associated with malformations of the heart (Putschar) Splenic gonadal fusion occurs in two forms "Continuous in which the main spleen is connected by a cord of splenic and fibrous tissue to the gonadal mesonephric structures and discontinuous in which discrete masses of splenic tissue are found fused to these same structures" (Putschar) In traumatically ruptured spleen splenic tissue in small nodules may grow as implants on the peritoneal surface. These nodules form capsules but lymphoid aggregates with a central arteriole will not be present (Cohen) (Fig 801)

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Chapter 21

BONE AND JOINT

INTRODUCTION

FRACTURES

Changes in Bone Produced by Nails, Screws, and Prostheses

OSTEOMYELITIS

ASEPTIC (AVASCULAR) BONE NECROSIS

Osteochondritis Dissecans

LETTERER-SIWE DISEASE, HAND-SCHULLER-CHRISTIAN DISEASE, AND EOSINOPHILIC GRANULOMA

CLASSIFICATION AND DISTRIBUTION OF BONE TUMORS

BENIGN TUMORS AND NONNEOPLASTIC LESIONS

Metaphyseal Fibrous Defects (Nonosteogenic Fibroma)
Fibrous Dysplasia
Osteoid Osteoma
Chondroblastoma, Osteochondroma, and Enchondroma
Bone Cyst
Benign and Malignant Rare Tumors
Osteochondroma, Enchondroma, Giant Cell Tumors (see Malignant Tumors)

MALIGNANT TUMORS

Laboratory Findings
Biopsy: Incisional, Aspiration, Frozen Section
Osteosarcoma
Chondrosarcoma, Osteochondroma, and Enchondroma
Clinicopathologic Correlation
Giant Cell Tumor (Benign and Malignant)
Fibrosarcoma
Ewing's Tumor
Reticulum Cell Sarcoma
Plasma Cell Tumor
Metastatic Tumors

MISCELLANEOUS CONDITIONS

Paget's Disease
Myositis Ossificans
Melorheostosis

GANGLION

GIANT CELL TUMOR OF TENDON SHEATH

Benign Giant Cell Tumor of Tendon Sheath (Xanthogranuloma, Fibrous Xanthoma, Myeloplaxoma; Benign Synovium)

PIGMENTED VILLONODULAR SYNOVITIS AND BURSITIS
SYNOVIAL OSTEOCHONDROMATOSIS
ARTHRITIS
Degenerative Joint Disease (Osteoarthritis)
Rheumatoid Arthritis

INTRODUCTION

Surgical pathology of bone in the United States is in the embryonic stage of development The European pathologists have studied bone thoroughly, their knowledge for the most part having come from thorough study of various bone lesions seen at postmortem examination The student need only examine German pathology books or Henke Lubarsch to realize how extensive has been their study The usual autopsy in the United States gives little or no attention to bone an autopsy is considered to be thorough if small segments of femur, vertebra and sternum are removed In most instances only a fragment of vertebra is examined even this specimen may not be studied microscopically American pathologists should study bone more thoroughly The routine removal at autopsy of rib the anterior half of the vertebral column, femur, and even humerus would prove worth while. The correlation of roentgenographic and microscopic findings in large sections of bone would add to the understanding of osseous pathologic processes. Recent excellent books on bone pathology should prove helpful (Aegerter Jaffe)

Primary neoplasms of bone are rare Their rarity plus the technical difficulty of section preparation has obscured the diagnosis and proper treatment of bone tumors. There are only a few centers in this country where much bone material is seen consequently many pathologists and radiologists have little practical knowledge of these tumors Before making a diagnosis it is imperative that the clinical history be complete that x ray examination be adequate and that the pathologic material be well prepared and representative of the lesion. In most instances the clinical story is not diagnostic. The radiologic pattern may be diagnostic in some, but there are so many exceptions that to rely on roentgenographic diagnosis without pathologic confirmation is hazardous. The article by Brailsford insisting that radiologic diagnosis invariably is diagnostic and that the pathologic diagnosis is not necessary is extremely dangerous propaganda not based on fact Radiologic examination must be thorough often roentgenograms of other bones are necessary The biopsy material must be representative adequate and well prepared Pathologists should not attempt to interpret poorly prepared slides

Too often poorly prepared and incorrectly diagnosed slides are referred for diagnosis by otherwise experienced pathologists. The reasons are obvious most technicians do not know how to prepare and stain bone sections properly many surgeons submit inadequate biopsies and the pathologist until recently has found little to help him in the literature (Bennett) Complicated classifications of bone tumors and bewildering discussions of embryology confuse him Most important, it must be realized that bone is plastic and that its reactions to injury tumor (benign or malignant) and metabolic conditions may merely vary in degree The

pathologist must orient himself with a thorough knowledge of the histology and development of bone (Maximow) He must know how to tell living bone from dead bone (Fig 802) and bone production from bone destruction (Fig 803) once he has established these fundamental properties of bone clearly in his mind, he can help the orthopedic surgeon select representative material for biopsy, decalcify the specimen with care, stain the sections properly, and correlate the microscopic findings with the clinical history and radiograms (Luck) The surgical pathologist must have all data before attempting a diagnosis if he does not, he may incorrectly diagnose an exuberant callus as an osteogenic sarcoma. We have seen instances in which a large piece of bone was submitted, good sections were made, but no significant pathology was seen. A review of the x ray examination demonstrated that the surgeon had biopsied bone adjacent to the pathologic lesion. *In our laboratory we refuse to make a diagnosis on poorly prepared outside slides*, and in the absence of roentgenograms. These two items are of primary importance, but the clinical history is also of value.



Fig 802 —Photomicrograph of dead bone with empty lacunae and ragged bone margins. (×270) (W U neg 49-5373)

Fig 803 —Appositional bone growth proceeding on the surface of a spicule of dead bone. The living bone is sharply demarcated and its lacunae contain nuclei. (×300) (W U neg 49 5640)

Brief descriptions will be made of some of the fundamental processes of bone *Dead bone* can be recognized by its staining reactions it stains a deeper blue than normal. Lacunar cells are absent and the margins of the bone are ragged (Fig 802) *New bone* formation can be recognized by the presence of well-stained small spicules of bone with cells in their lacunae and osteoblasts along their margins (Fig 803) The stroma between such new bone will be active. New bone formation can be studied in a variety of pathologic processes such as fibrous dysplasia, after a fracture, and in osteitis fibrosa cystica. As this bone becomes older it becomes calcified *Bone destruction* can be recognized by the presence of large multi

nucleated cells called osteoclasts which are present on the ragged margins of bone that is being destroyed. Some of this bone will already be partially dead bone. The osteoclasts and the osteoblasts are probably closely related, and it is possible that the osteoblast of today will become the osteoclast of tomorrow (Willis).

The diaphysis of the bone is its shaft. The epiphysis represents the growing extremity of a bone. When a bone has reached its adult length the epiphysis closes. Enchondral ossification occurs at the epiphysis in a growing bone. Longitudinal, regularly spaced columns of vascularized cartilage are replaced by bone. When this process finally ends the epiphysis becomes calcified and ossified. The time of closure of the epiphysis differs in various bones and in the sexes. Whether the epiphysis is closed or open influences the extension of pathologic processes. For instance cartilage is often a barrier to spreading osteosarcoma. If the epiphysis is closed and cartilage is no longer present, the bone is more easily invaded. An understanding of the blood supply of bone helps to explain spread and limitation of infection, the healing of fractures, and the involvement of bone by primary or secondary neoplasms. The metaphysis is supplied by nutrient end arteries entering from the diaphysis. These vessels terminate at the epiphyseal plate. Vessels also enter from the periphery. The epiphyses receive their blood supply from widely anastomosing vessels. Diaphyseal cortex is supplied by vessels entering through Volkmann canals which communicate with the haversian system. A nutrient artery enters the medullary canal at about the center of the shaft, divides, and extends both distally and proximally. The metabolic exchange of calcium and phosphorus occurs primarily in the metaphysis.

The localization of various pathologic processes occurs in different areas of the same bone and in different bones at different ages. The biologic reasons for such localizations are often unknown but it is important for the pathologist to be able to answer certain questions about a given lesion of bone. What bone or bones are involved? In what part of the bone is the lesion located? Is it a localized or a diffuse process? What is the age and sex of the patient? As an example of how to apply these questions let us take a lesion in a 13 year-old boy located in the tibia in its diaphyseal area. It is an eccentric, sharply delineated lesion. There are no other lesions in other bones. The localization of this lesion rules out the simple bone cyst which usually arises in the metaphysis. The patient is too young to have giant cell tumor. In fact there is only one lesion which will fit in this case, the metaphyseal fibrous defect of Hatcher (Fig 820). This diagnostic approach should be used for all bone lesions; in many instances it will resolve the problem without difficulty.

The *periosteum* is closely applied to bone and is a modified connective tissue; however periosteum has special properties. It may become detached and elevated from the bone in such pathologic processes as trauma, infection, and primary or secondary malignant tumor. Under certain conditions its elevation causes periosteal bone proliferation. New bone formation between the elevated periosteum and the bone may be seen by radiographic examination as fine spicules placed perpendicular to the long axis of the bone. This finding, to the inexperienced radiologist and surgeon, is often considered a manifestation of a malignant neo-

plasm. We have seen conspicuous periosteal bone proliferation in syphilis, tuberculosis metastatic carcinoma osteosarcoma, Ewing's tumor, and even after trauma (Fig 804) In some instances such as plasma cell myeloma, the periosteum may be destroyed or encroached upon so that no radiographic changes occur If a section of periosteum is transplanted beneath the capsule of a kidney of an experi



Fig. 804—Extreme periosteal new bone formation occurring in the mandible after a hematoma had almost completely destroyed the bone through interference with blood supply Only fragments of dead mandible remain, but the exuberant periosteal bone proliferation is extending from the periosteum in long columns (Upper photograph low power W U neg 52 3874 Lower photograph ×150 W U neg. 52 3875)

mental animal its independent property of forming bone can be demonstrated (La Croix) Nerve filaments are present in the periosteum and carry proprioceptive and sensory impulses Small nerve filaments may also pass with the nutrient vessels into the medullary canal

FRACTURES

Fractures are breaks in the continuity of bone with severance of periosteum blood vessels and perhaps muscles The return of bone to normal following fracture depends upon factors such as treatment the age of the patient the severity



Fig 805 — Exuberant callus formation following fracture. (Courtesy Dr John Morton Strong Memorial Hospital Rochester N Y)

of the fracture the vascularity of the area and the nutrition of the patient (Fig 805) Fractures fail to heal because of improper immobilization complete devascularization of segments of the fractured bone persistent infection and the interposition of soft tissue between the ends of the bone. A hematoma forms between the two severed ends of bone. This hematoma is extremely important in fracture healing Organization of this hematoma begins with the ingrowth of young capillaries This granulation tissue is highly cellular initially but undergoes

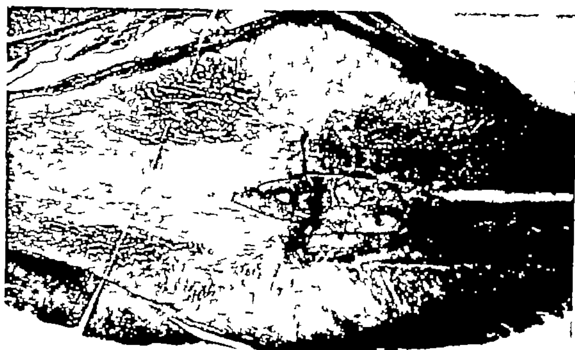




Fig 806.—Healing fracture of a long bone in a rat at 7 days Note intact periosteum and intramembranous bone formation. (Low power) (W U neg 52-4346.) (Slide contributed by Dr Richard Odell St. Louis, Mo.)

Fig 807.—Detailed view of the point of fracture. Granulation tissue has been replaced with cartilage and new bone is gradually replacing this cartilage. A fragment of dead bone within the marrow cavity is being reabsorbed. (Low power) (W U neg 52-4344) (Slide contributed by Dr Richard Odell St. Louis Mo.)





Fig 808—Healing fracture of a long bone in a rat at 3 weeks. (Low power) (W U neg. 52-4345) (Slide contributed by Dr Richard Odell, St Louis, Mo.)

Fig 809—Detailed view of fracture site shown in Fig 808 Bone has almost completely bridged the gap. A small amount of cartilage can still be seen near the dead bone fragments (Low power) (W U neg 52-4344) (Slide contributed by Dr Richard Odell St. Louis Mo.)

maturation with decrease in cellularity and begins to form fibro- and hyaline cartilage at its periphery The cells covering the bone close to the fracture die. After about three days the devitalized bone fragments begin to be reabsorbed Intramembranous bone growth makes its appearance from the cambium layer of the periosteum, both proximal and distal to the fracture site (Figs. 806 and 807) The newly formed trabeculae begin to calcify as the cartilage is replaced by bone. This process extends on each side of the fracture until the two areas meet to form the primary callus. The periosteum is composed of an outer fibrous layer and an inner osteogenic layer (Ham) This inner osteogenic layer and the endosteum contribute to the formation of callus. "Lines of stress through the fracture site do not dictate the alignment of trabeculae in the primary callus" (Luck) The secondary callus is made up of mature lamellar bone. The primary callus is absorbed. The new bone is laid down predominately along lines of stress (Figs. 808 and 809) The early reduction of fractures promotes rapid healing (Murray) With proper reduction of the fracture adequate blood supply no infection and normal metabolism, the fracture heals rapidly with little visible callus. Exuberant *callus usually means slow fracture healing* Delayed manipulation causes perpetuation of the hyperemia, formation of new granulation tissue osteoporosis, and local tissue acidity—factors incompatible with calcification and ossification (Luck) In children even with prominent angulation or deformity the bone remodels itself to an astonishing degree (Blount Odell) For this reason open reduction and internal fixation of fractures in children are seldom justified Shortening of a long bone due to overriding of fragments will nearly always correct itself by overgrowth of bone.

The sequence of events which take place in a rapidly forming primary callus with exuberant cartilage formation and disorderly membranous bone formation may provide a bewildering pattern on microscopic examination. The microscopic picture may be difficult to differentiate from osteosarcoma.

Changes in Bone Produced by Nails, Screws, and Prostheses

If a noncorrodible nail such as a Smith Petersen nail is driven into a bone to support an area of fracture, this nail eventually is completely sequestered. The nail is separated from the medullary cavity by fibrous tissue which is continuous with the periosteum. Bone similar to cortical bone forms in the tract next to the fibrous tissue (Fig 810) This cortical bone in turn forms an uninterrupted continuity with the cortex of the bone No foreign body giant cell reaction is observed (Collins, 1953) The changes produced by acrylic Judet type prostheses are similar to those produced by the Smith Petersen nail. This material is apparently inert (Collins 1954)

OSTEOMYELITIS

Osteomyelitis can be caused by practically any bacteriologic agent about 90 per cent of the cases are caused by the coagulase-positive staphylococci Other organisms such as the streptococcus, pneumococcus gonococcus, and meningococcus and rare organisms such as Brucella and *Histoplasma capsul*

cause it Osteomyelitis may occur after compound fractures The highest percentage of hematogenous infections occurs in patients under 20 years of age About 75 per cent of cases occur in the lower extremity The changes in the bone are conditioned by the bone involved, the virulism of the organism, resistance of the host, and many other factors Frequently the adjacent joint is involved If prominent pathologic alterations occur in joints and bone, the bone completely recovers, but not the joint Whether the infection be hematogenous or introduced by trauma or operation, the pathologic process is the same Advanced lesions often seen in



Fig 810—Photomicrograph demonstrating sequestration within a nail tract. The lower margin shows fibrous tissue next to the nail continuous with periosteum. The inner bone formation is continuous with the cortical bone (Low power) (W U neg 58-4088)

the past are infrequent today because of antibiotics. The metaphyseal area is the commonest zone involved In the metaphysis the vessels are end vessels and the process is therefore localized unless it extends into the adjacent marrow cavity Infection of the epiphysis although rare, may spread quickly from it into the adjacent joint because of widespread vascular anastomoses. The introduction of the strong antimicrobial drugs led initially to the treatment of acute hematogenous osteomyelitis without open drainage or saucerization. The mortality and morbidity dropped precipitously after the use of these drugs However more recently saucerization and drainage have been instituted in combination with antibiotics to treat acute osteomyelitis and have resulted in further improvement of results. The frequency of late recrudescence of osseous infection has been much less The

combined surgical and drug therapy has also proved much more effective in treating the staphylococcal infections which prove to be partially or totally resistant to antibiotic therapy Infections of the latter type appear to be increasing in frequency

The sequence of events varies in its speed of evolution. If the infection is massive, the inflammatory process in the metaphyseal area is complicated by an infected thrombus leading to infarction and subsequent destruction of bone. The infectious material invades the cortex through the vessels of the Volkmann canals. The infection of course may spread through the medullary canal through the cortex or into the joint space. It spreads beneath the periosteum and may extend into the joint space. If pus develops beneath the periosteum, perforation through it usually takes place. *With the process tending to localize, the cambium layer of the* periosteum responds to the presence of dead bone (the sequestrum) by forming new bone (the involucrum) The involucrum eventually extends around the entire bone (Figs. 811 and 812) The sequestrum, if not too large may be extruded through cutaneous sinuses. Chronic osteomyelitis may show prominent periosteal bone proliferation (Fig 813) Osteomyelitic sinuses may become lined by squamous epithelium which may extend deeply into the bone. Long standing squamous lined sinuses which extend into the bone may become discontinuous with the cutaneous surface. Despite apparent healing of the overlying skin large epidermal inclusion cysts slowly develop in the underlying bone. These contain trapped keratinized debris similar to epidermal inclusion cysts of the skin Rarely squamous carcinoma develops within these sinuses. More rarely, sarcoma occurs about them.

The chronic osteomyelitis persists as long as infected dead bone remains The dead bone is surrounded by granulation tissue, which attacks the sequestrum making it pitted on the surface next to the marrow cavity the cortical surface remains smooth. At the proper time operative removal of the sequestrum usually allows the osteomyelitis to heal. The osteomyelitis may recur many years later if bacteria remain within the scar

Tuberculous osteomyelitis is a hematogenous infection usually seen in young adults or children. Wherever pasteurization of milk is mandatory the incidence of bone tuberculosis is low The bones most commonly infected are the vertebra, bones of the hip knee, ankle, elbow and wrist (Luck) Tuberculosis usually involves the metaphyseal area the epiphysis and the synovium. There has been considerable controversy concerning the area primarily involved. Metaphyseal infection is common in children and epiphyseal infection in adults. This does not have too much significance, for all zones eventually become involved (Fig 814) Tuberculous granulation tissue forming in the synovia separates it at its points of attachment the cartilage no longer nourished from the synovia, undergoes progressive destruction allowing tuberculous granulation tissue to extend into the epiphysis and finally into the metaphyseal area. If the process begins in the epiphysis the tuberculous granulation tissue extends into the adjacent joint. Conversely when the process begins in the metaphyseal area, extension into the joint may be heralded by the development of fluid within it. Cutaneous sinuses can

Fig 811.—Roentgenogram of chronic osteomyelitis of the fibula. Note the dense irregular bone. (W U neg 50-1495)

Fig. 812.—Resected fibula showing dense outer involucrum surrounding the loosened sequestrum with its pitted surface (W U neg 50-652.)

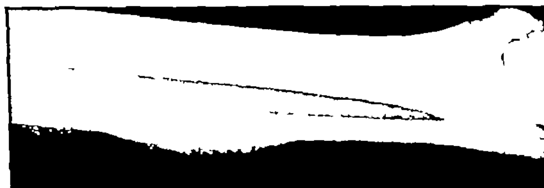


Fig 813.—Roentgenogram of prominent periosteal bone proliferation in chronic osteomyelitis. (W U neg 51 1883)



Fig 814 —Extensive involvement of synovium of the elbow joint by tuberculous granulation tissue. (W U neg 49-978.)



Fig 815 —Roentgenogram of luetic knee joint with defects in the bone and periosteal bone proliferation. (W U neg 49 3940.)

occur in advanced diseases These sinuses allow entry of secondary bacterial inf tion which modifies the pathologic changes. When the tuberculous process beg to heal, fusion of the joint may occur with complete or partial denudation cartilage and kissing sequestra." Sequestra are cortical in pyogenic proces but in tuberculous disease they are cancellous Tuberculosis of the diaphysis a occurs (Carrell) The pathologic changes in tuberculosis of bone have b greatly modified by antimycobacterial drugs. Tuberculous tenosynovitis of hand may form multiple soft tissue masses that may be mistaken for neopla (Mason)

Tertiary syphilis may involve the bone and cause both bone destruction a bone production it frequently is associated with conspicuous periosteal bone p liferation (Westermark) (Fig 815) The necrotic well-defined defects are ma cortical and periosteal and are surrounded by sclerotic bone. These bone lesi may be in the vertebrae flat bones of the hands and feet, and in the diaph of the long tubular bones If a single x ray is taken a diagnosis of osteosarco may be made Biopsy will show a granulomatous process with bone destruct and production The diagnosis usually will be apparent if multiple films of bones are studied. In single or isolated lesions the diagnosis may be difficult presence of a positive serology does not eliminate the possibility of osteosarco In such instances a biopsy is required to make an exact diagnosis. We have s osteomyelitis caused by Brucella *Histoplasma capsulatum* and Actinomyces

ASEPTIC (AVASCULAR) BONE NECROSIS

Osseous aseptic necrosis is an important orthopedic pathologic abnorma which has been reported as osteochondritis in practically every secondary epiph and many primary epiphyses (Fig 816) Unfortunately each site has been scribed independently and often given individual names such as

Tibial tubercle (Osgood-Schlatter disease)
Osgood, 1903
Patella—primary epiphysis
Kohler 1908
Tarsal navicular
Kohler 1908
Capital epiphysis femur (osteochondritis deformans juvenilis
Legg Perthes disease)
Legg 1909
Head of humerus
Lewin, 1930

The etiology of many cases is unknown and is thought possibly to be tr matic or related to endocrine imbalance. In some etiology is related to oblite tion of the epiphyseal blood supply because of fracture or dislocation. Phemis clarified the pathogenesis of femoral head avascular necrosis secondary to co plete interruption of blood supply occurring in fractures of the femoral neck. T sequence of events implies death of the epiphysis which in time becomes m clearly seen roentgenographically Thus death of bone is followed by hyperer of the neighboring bone elements. The overlying cartilage of the epiphysis m or may not remain viable, for it receives nourishment from the overlying synovi

The dead bone gradually undergoes resorption. There may be osteoclasis on one side of necrotic trabeculae, with osteoblastic activity on the other (Luck) Thus bone is gradually replaced by "creeping substitution" This replacement of the dead epiphysis by new bone is a slow process, taking months or even years. The new soft bone may flatten because of pressure. If this change occurs, degenerative joint disease soon follows.



Fig 816.—Aseptic bone necrosis in the head of the femur Note fibrillation and complete absence of cartilage. Subchondral bone is dead with empty lacunae. (Low power) (W U neg 52-4090)

Osteochondritis Dissecans

Osteochondritis dissecans is a small area of necrosis in the articular cartilage, and usually with subchondral bone which totally or partially separates from adjacent structures The etiology is uncertain but is probably related to trauma. It occurs most frequently on the medial femoral condyle near the intercondylar notch (Luck)

LETTERER-SIWE DISEASE, HAND-SCHÜLLER CHRISTIAN DISEASE, AND EOSINOPHILIC GRANULOMA

Letterer-Siwe disease is rare it occurs predominantly in children under the age of 2 years and is associated with skin manifestations visceral involvement wide dissemination of the process, and 100 per cent fatality Hand-Schüller Christian disease does not involve the skin but frequently attacks many bones, particularly the long bones and the skull. It often affects the pituitary gland

causing diabetes insipidus. Exophthalmos may be present and lesions in the lung are common This entity may cause death.

Eosinophilic granuloma the most common and mildest manifestations of this group occurs in young adults and the prognosis is good In our 24 cases 15 were male 9 were female, 13 were 10 years of age or younger and the oldest was 29 (McGavran) Any bone can be involved with the possible exception of the bones of the hands and feet Usually only one bone is affected The most common sites of involvement are the cranial vault, ribs, vertebrae and particularly the humerus and femur (Jaffe) Cases have been reported with increasing frequency since the initial articles by Otani Green Jaffe and Hatcher None of our cases (24) progressed to Hand Schüller Christian disease



Fig 817 —Osteolytic lesion of the skull in a woman 40 years of age. This lesion was thought to be metastatic carcinoma radiographically but proved to be a solitary lesion of eosinophilic granuloma. (W U neg. 48-4331)

Radiographically eosinophilic granuloma is an osteolytic lesion often in the metaphyseal area of long bones which may be associated with periosteal bone proliferation (Hatcher) In one of our patients, a young woman 25 years old a single osteolytic lesion of the skull was thought to be metastatic carcinoma but proved to be eosinophilic granuloma (Fig 817) This process in the femur of a young adult may suggest Ewing s sarcoma (Fig 818)

These diseases are impossible to differentiate by microscopic study of bone sections Their separation must be based upon the clinical manifestations, the age of the patient, and the distribution of the lesions. Grossly the tissue is often yellow Gerstel felt *that transition could* be traced *from the* beginning granulomatous lesions without foamy cells to an end stage of healing by fibrosis. Eosinophils are prominent in the early stages of the process thus the name eosinophilic granuloma. Giant cells may be present (Fig 819) The diagnosis

TABLE 40 CLASSIFICATION OF BONE TUMORS*

	BENIGN TUMORS OF BONE	MALIGNANT COUNTERPART (IF ANY)	MALIGNANT TUMORS OF BONE (ARISING THROUGH MALIGNANT CHANGE OR INDEPENDENTLY)
Of cartilage cell or cartilage-forming connective tissue derivation	Peripheral osteocartilaginous exostosis (multiple exostosis) (Osteochondroma)	Peripheral chondrosarcoma	Chondrosarcoma
	Central: Enchondroma (skeletal enchondromatosis)	Central chondrosarcoma	
	Central: Benign chondroblastoma	Not known	
	Central: Chondromyxoid fibroma	Not known	
Of osteoblastic derivation	Osteoma		Osteosarcoma
	Osteoid-osteoma	Not known	
	Osteogenic fibroma	Not known	
	Other osteoid tissue-forming tumors	Osteosarcoma	
Of nonosteoblastic connective tissue derivation	*Metaphyseal fibrous defect* (nonosteogenic fibroma)	Not known	
	Giant cell tumor	Malignant giant cell tumor	Fibrosarcoma
Of mesenchymal connective tissue origin	———	Fibrosarcoma	Ewing's sarcoma
Of hematopoietic origin	———	———	Plasma cell myeloma; Malignant lymphoma (Reticulum cell sarcoma, Lymphosarcoma, Hodgkin's disease)
Of nerve origin	Neurofibroma; Neurilemoma	Malignant schwannoma (Neurogenic fibrosarcoma)	
Of vascular origin	Hemangioma	Hemangioendothelial sarcoma	(*Hemangioendothelial sarcoma*)
Of fat cell origin	Lipoma	———	Liposarcoma
Of notochordal derivation	———	———	Chordoma
Of adamantine or possibly basal cell derivation	———	———	So-called adamantinoma

*After Lichtenstein, L.: Cancer 4: 335-341 1951 (Modified.)

may become obscured by the periosteal bone proliferation associated with fracture (Hatcher) Rarely, after fracture, this process may extend into adjacent soft tissues (Otani) We have seen two soft tissue recurrences after surgery which disappeared with irradiation These lesions may spontaneously regress but are radiosensitive and radiocurable with small amounts of irradiation



Fig 818—Roentgenogram of osteolytic lesion of the femur in a boy 12 years of age This was thought to be Ewing's tumor but proved microscopically to be eosinophilic granuloma. (W U neg 48-6045)

Fig 819—Photomicrograph of eosinophilic granuloma of bone with numerous fat filled macrophages eosinophils and scattered giant cells. (×400) (W U neg. 50-3755)

CLASSIFICATION AND DISTRIBUTION OF BONE TUMORS

The classification of bone tumors is usually so highly complicated that it has served only to discourage the embryo pathologist. In the classification by the American College of Surgeons osteosarcoma has many unjustified subvarieties. Unfortunately the thorough study of any osteosarcoma discloses several varieties in the same neoplasm. The classification based on histogenesis which Lichtenstein has devised receives our approval (Table 40)

At Barnes Hospital there is an extremely active orthopedic service with many referred cases The distribution of 146 bone tumors seen in a little over a four year period is rather characteristic with the possible exception of a disproportionate number of chondrosarcomas. The commonest benign bone tumor is the osteochondroma, and the commonest malignant bone tumor is the metastatic carcinoma. Fibrous dysplasia and metaphyseal fibrous defect probably should not be included (Table 41)

TABLE 41 DISTRIBUTION OF 146 BONE TUMORS JULY 1948 TO MAY 1952 BARNES HOSPITAL, ST LOUIS MO

NUMBER	TYPE OF TUMOR	LOWER EXTREMITY	UPPER EXTREMITY	TRUNK	SKULL
	Benign				
37	Osteochondroma	22	14	1	
8	Fibrous dysplasia	2	1	3	2
7	Osteoid osteoma	7			
6	Metaphyseal fibrous defect	5	1		
6	Giant cell tumor		1	1	4
3	Chondroblastoma	3			
3	Enchondroma	1	2		
70		40	19	5	6
	Malignant				
17	Metastatic carcinoma	5	1	8	3
16	Osteosarcoma	9	4	2	1
16	Chondrosarcoma	5		11	
10	Ewing's tumor	3	2	5	
6	Multiple myeloma		1	5	
6	Reticulum-cell sarcoma	5		1	
4	Fibrosarcoma	4			
1	Plasmocytoma			1	
76		31	8	33	4

BENIGN TUMORS AND NONNEOPLASTIC LESIONS

Metaphyseal Fibrous Defects (Nonosteogenic Fibroma)

This distinctive lesion of bone occurs in adolescents most commonly in long tubular bones often lower femur or upper or lower tibia. It is an eccentric sharply delimited lesion, not too distant from the epiphysis (Fig 820) It may involve the entire width of bones such as the fibula. Fourteen of 45 cases reported by Hatcher had concomitant epiphyseal disorders. Because of this association Hatcher doubts that it is a true neoplasm. Furthermore several facts indicate, according to Cunningham that the lesion arises as the result of some developmental aberration at the epiphyseal plate

1 It has been found only in the metaphysis of a bone
2 It migrates (relatively) away from the epiphysis as the bone grows in length
3 It tends to be elongated in the longitudinal axis of the bone, as though the abnormal development had occurred over a period of time
4 Ponsetti and Friedman have illustrated three successive lesions arising from the same area of the epiphyseal plate indicating that the factors producing the defects may act intermittently
5 No evidence of malignant transformation or unusual mitotic activity has been noted.

Microscopically it consists of cellular whorllike masses of fibrous tissue (Fig 821) Scattered giant cells and small collections of foam cells may be seen. It differs from fibrous dysplasia because it does not form bone. We have seen it diagnosed incorrectly as fibrosarcoma. It has never been reported as becoming malignant. Clinically there are few or no symptoms except pain The lesion is usually found incidentally on x ray examination. We have seen several fractures occurring through the thinned cortex.

Fibrous Dysplasia

Fibrous dysplasia, a nonneoplastic condition, can be divided into two types: the monostotic and polyostotic. The monostotic variety occurs frequently in older children and young adults and affects most commonly the rib, femur, tibia, and maxilla. Involvement of the maxilla or mandible formerly was called fibrous osteoma (Phemister). Monostotic fibrous dysplasia in the long bones is frequently

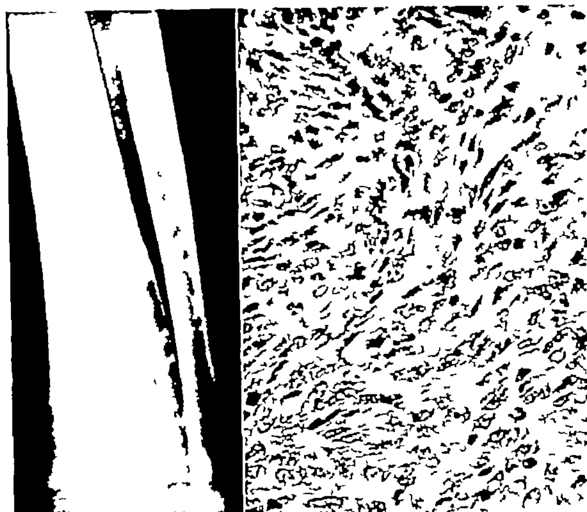


Fig. 820.—Roentgenogram of metaphyseal fibrous defect (nonosteogenic fibroma) of the lower end of the tibia. Note its sharp delineation and sclerotic margins. (W. U. neg. 52-3782.)

Fig. 821.—Photomicrograph of an area of metaphyseal fibrous defect demonstrating cellular whorllike masses of fibrous tissue. (×400.) (W. U. neg. 52-3453.)

associated with a history of trauma (Schlumberger). The polyostotic type (an unusual variant) usually is associated with endocrine dysfunction, precocious puberty in females, and areas of pigmentation (Albright). There is frequently a unilateral distribution of these lesions. Schlumberger feels that the two types of fibrous dysplasia are unrelated although they cannot be separated by examination of a single bone grossly or microscopically.

Roentgenograms of these lesions in the rib show a fusiform expanded mass with thinning of the cortex. In the tibia a lobulated, sharply delimited lesion of

the shaft is formed (Fig 822) Comparable lesions in membranous bone, particularly in the maxilla or mandible, may show an overgrowth of dense bone.

The tissue cuts with a gritty consistency and is grayish yellow (Fig 823) The cortical bone often is thinned and expanded Microscopically narrow curved, misshapen bone trabeculae usually are interspersed with fibrous tissue of variable

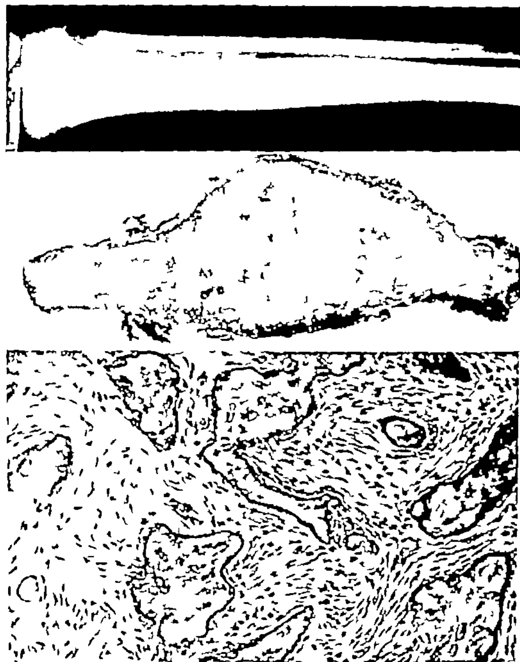


Fig 822 —Roentgenogram of fibrous dysplasia of the tibia forming a sharply delimited lesion. (W U neg 49 5849)

Fig 823 —Gross photograph of fibrous dysplasia of the rib forming a fusiform expanded mass which is grayish yellow in color (W U neg. 49-4574)

Fig 824 —Photomicrograph of typical fibrous dysplasia of the rib demonstrating spicules of new bone formation with intervening cellular fibrous tissue. (×140) (W U neg 52-335.)

cellularity (Fig 824) Highly cellular areas may be diagnosed incorrectly as sarcoma. The osseous metaplasia is close to pre-existing bone. Focal areas of hyaline cartilage (Lichtenstein) and small areas of cyst formation may be present The transition of normal to abnormal bone is often abrupt this is helpful in differentiating it radiographically from osteitis fibrosa cystica due to hyperparathyroidism. This lesion seldom undergoes malignant change (Perkinson)

Resection cures in bone such as rib, curettement is adequate in long bones such as tibia, indeed in the maxilla where some deformity may exist, partial removal of the lesion is all that is necessary We have seen one remarkable lesion of the polyostotic type in which a huge overgrowth of tissue from a rib extended into the pleural cavity and caused pulmonary symptoms. Over 1 000 grams of tissue were removed.

Osteoid Osteoma

Osteoid osteoma is a benign neoplasm of bone occurring in males about twice as often as in females It is found most frequently in patients between 10 and 30 years of age. This lesion should not be confused as it has in the past with a local area of chronic osteomyelitis (Brown) It has been reported in practically every bone but occurs most frequently in the tibia, humerus, fibula, femur, and vertebra. It usually begins either in the spongiosa the cortex or rarely in the subperiosteal tissues of the metaphysis The central nidus of this tumor seldom is larger than 1.5 cm. and is surrounded by an area of dense bone (Fig 825) When the lesion appears in the cortex, the area of reaction may extend for several centimeters along the bone as well as around it (Fig 826)

Microscopically the lesion is sharply delineated and made up of more or less calcified osteoid growing within highly vascular osteoblastic connective tissue and surrounded by dense bone (Figs. 827 and 828) There is no evidence of inflammation. We have seen one osteoid osteoma of a vertebra misdiagnosed as an osteosarcoma. If the lesion is removed piecemeal, it can still be diagnosed because of the characteristics of the nidus (Fig 828)

The most prominent symptom is increasing pain often well localized. Clinical and laboratory evidence of infection is lacking If the lesion is in the cortex of the bone, a diagnosis of Garré's osteomyelitis may be made because of the adjacent bone reaction. Removal of the lesion relieves symptoms.

Dahlin reported a benign tumor designated as giant osteoid osteoma In his 11 cases the most common site was the vertebra (4) 5 were in long bones Lichtenstein has proposed the term benign osteoblastoma for this entity This lesion can become 5 cm. in diameter and bears a very close microscopic resemblance to the well known small osteoid osteoma. It has been mistaken for osteosarcoma.

Chondroblastoma, Osteochondroma, and Enchondroma

Chondroblastoma of bone is often confused with giant cell tumor, but is much rarer and bears no relation to this lesion It was classified in the past with other giant cell tumors as the chondromatous variant (Codman) This tumor occurs particularly in males under 20 years of age. It occurs in the epiphyseal end of



Fig 825 —Roentgenogram of osteoid osteoma of the talus. Note small central osteolytic nidus surrounded by dense bone. (W U neg 48-3921)

Fig 826 —Roentgenogram of osteoid osteoma of the femur obscured by an area of reacting bone extending up as well as around the bone Such lesions in the past were often diagnosed as Garré's osteomyelitis (W U neg 50-1910)

Fig 827 —Photomicrograph of a well-defined nidus of an osteoid osteoma. (×15) (W U neg 54 5990)

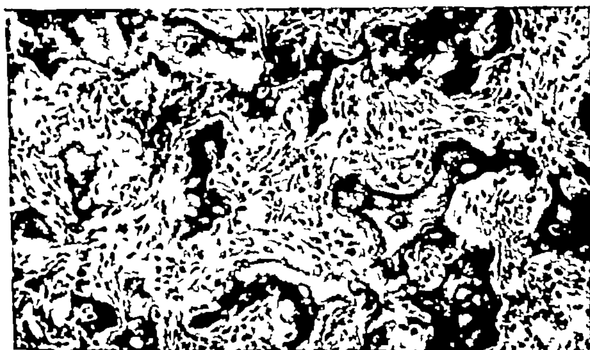


Fig 828 —Photomicrograph of variably calcified osteoid growing within highly vascular osteoblastic connective tissue These changes are typical of osteoid osteoma. (Moderate enlargement.) (W U neg 52-4539)



Fig 825 —Roentgenogram of osteoid osteoma of the talus. Note small central osteolytic nidus surrounded by dense bone. (W U neg 48 3921)

Fig 826 —Roentgenogram of osteoid osteoma of the femur obscured by an area of reacting bone extending up as well as around the bone Such lesions in the past were often diagnosed as Garré's osteomyelitis. (W U neg 50-1910)

Fig. 827.—Photomicrograph of a well-defined nidus of an osteoid osteoma. (×13.) (W.U. neg. 54-5990.)

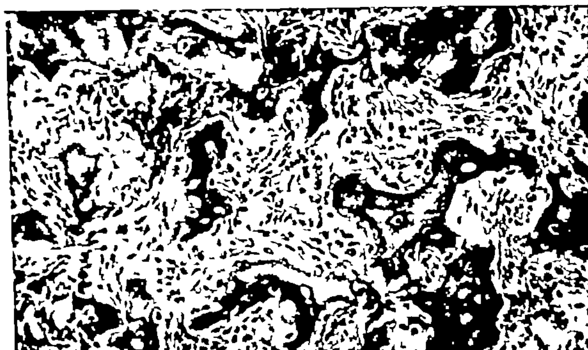


Fig. 828.—Photomicrograph of variably calcified osteoid growing within highly vascular osteoblastic connective tissue. These changes are typical of osteoid osteoma. (Moderate enlargement.) (W.U. neg. 52-4539.)

long bones before epiphyseal cartilage has disappeared particularly in femur, tibia, and humerus (Figs. 829 and 830) We also have seen it involve small bones of the feet. This lesion in the past often was resected because of a diagnosis of chondrosarcoma. Radiographically the tumor usually is fairly well delimited, contains areas of rarefaction and may extend from the epiphysis into the metaphyseal area. Transarticular spread occurred in two of Valls cases. This lesion rarely may recur following curettage.



Fig 829 —Gross photograph of a well-outlined chondroblastoma involving the epiphysis of the humerus in a young adult. (Gross specimen contributed by Dr A. Ramus Manila, P I.) (W U neg 57-863)

Microscopically this lesion often is confusing because of its extreme cellularity and variability The occasional scattered collections of giant cells may lead to an erroneous diagnosis of giant cell tumor The basic cell is an embryonic chondroblast without sufficient differentiation to produce intercellular chondroid (Hatcher) It often is highly cellular and has closely packed polyhedral nuclei. These changes are mistaken for chondrosarcoma (Fig 831) The distinctive microscopic changes are small zones of focal calcification These zones range from faintly discernible

bluish areas to obvious calcification surrounded by giant cells. This lesion can be distinguished from giant cell tumor by the focal areas of calcification, and the absence of characteristic stroma of giant cell tumors

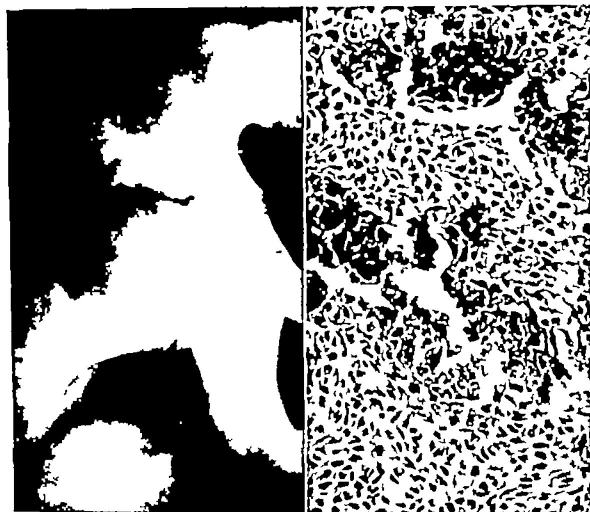


Fig. 830 —Roentgenogram of a chondroblastoma of the epiphyseal area of the head of the femur (W U neg 52 3398)

Fig 831 —Photomicrograph of a cellular area in a chondroblastoma with areas of focal calcification. (×300) (W U neg 57-4543)

Clinically patients with this lesion have pain which may become severe. Curettement is the indicated treatment. There is no evidence that this tumor becomes malignant or is ever primarily malignant as Geschickter contends. Hatcher's case of chondrosarcoma following heavy irradiation for chondroblastoma was caused by the heavy irradiation rather than malignant transformation of the tumor

Bone Cyst

Unicameral bone cysts occur in long bones most commonly in the upper portion of the shaft of the humerus and femur (Fig 832) Seventeen of James cases were in the humerus. These cysts occur predominantly in males (14 out of 19 cases in Jaffe's series) and almost all occur in patients under 20 years of age.

These lesions are usually advanced when first seen they are usually metaphyseal in position and do not involve the epiphysis. In time they tend to migrate away from the epiphysis (Stewart) The cortex is thinned and periosteal bone prolifera tion does not take place except in areas of fracture. These lesions often fracture, usually in the proximal portion of the cystic area (Jaffe) The cyst contains a clear or yellow fluid and is lined by a smooth connective tissue membrane which may be brown. Microscopically vascular connective tissue hemosiderin often



Fig. 832.—Roentgenogram of a typical unicameral bone cyst of the upper end of the femur abutting against the epiphyseal plate The patient was a 13-year-old boy (W U neg 49-5897)

within phagocytes, and cholesterol clefts are common. The diagnosis may be dif ficult in the presence of reparative changes following fracture, recurrence after bone grafting and when articular cartilage is included in the curettings. The diagnosis becomes clear if the history and x rays are available. Pommer believes that these cysts develop after mild trauma without fracture but with intramedul lary hemorrhage. Von Mikulicz, however believes that this lesion has its basis in a local disorder of development and bone growth. The latter theory is the more widely accepted. The treatment of choice is curettement and replacement of the cyst with bone chips. Treatment of these cysts may be correlated with their ac tivity Good results are obtained when the cyst has migrated away from the epi

physeal line, recurrences may appear if the cyst treated is lying close to the epiphyseal line (Stewart)

Aneurysmal bone cyst is a rare lesion that may be mistaken for a peculiar giant cell tumor a hemangioma, or even an osteosarcoma These large cystic lesions occur usually in patients between 10 and 20 years of age They occur mainly in the vertebra and flat bones, but can occur in the shaft of long bones (Dahlin)

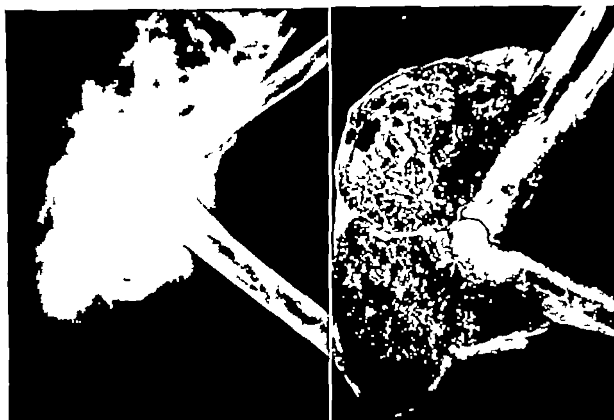


Fig. 833 —Roentgenogram of an aneurysmal bone cyst in the region of the elbow Functional disability forced resection.

Fig. 834 —Gross photograph of the cystic hemorrhagic aneurysmal bone cyst shown in Fig 833 (Courtesy Dr Louis Lichtenstein, Los Angeles, Calif)

Radiographically they show an eccentric expansion of the bone, erosion and destruction of the cortex and a small border area of periosteal bone formation (Figs. 833 and 834) Grossly they form a spongy hemorrhagic mass which may extend into the soft tissues and be covered by a thin shell of reactive bone. Microscopically large spaces filled with blood are seen often accompanied by numerous giant cells. The septa contain osteoid (Dahlin) (Fig 835) This lesion used to be confused with giant cell tumor but, unlike it it never becomes malignant The pathogenesis is unknown

Benign and Malignant Rare Tumors

Hemangiomas of bone are commonly reported in the vertebra as a postmortem finding In 2 154 autopsies studied by Töpfer hemangiomas occurred in 11 9 per cent they were multiple in 34 per cent Many of the lesions reported were

not true tumors. Hemangiomas in the long bones are extremely rare (Bucy) We have seen cavernous hemangioma of the clavicle and ribs. We have also observed a lesion of the fibula causing irregular bone destruction in the shaft, which was incorrectly diagnosed as Ewing's tumor When a lesion involves the flat bones, sunburst trabeculation radiates from a common center with elevation of the periosteum. These tumors may erode the cortex and occasionally may be multiple. On section they often have a currant jelly appearance. They do not undergo malignant change. Microscopically the appearance is classical with a thick walled latticelike pattern of endothelial lined spaces filled with blood. Rarely they may have a lymphangiomatous element.

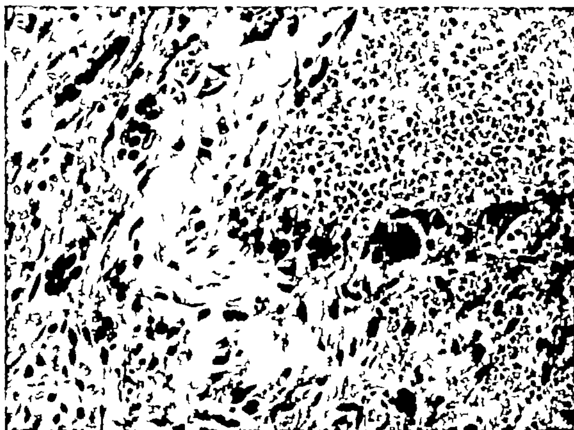


Fig 835 —Photomicrograph of aneurysmal bone cyst showing characteristic septum covered with giant cells and having osteoid within its substance. (×400) (W U neg 54-5987)

Chondromyxoid fibroma of bone is an unusual benign tumor often confused with chondrosarcoma. It was defined initially by Jaffe. The tumors usually occur in young adults, often in a long bone but they also have been reported in the small bones, the rib and vertebra. This lesion may become large. It is solid, yellowish white or tan in color replaces bone, and thins the cortex. It is highly cellular has a myxoid matrix contains areas suggesting cartilage and often has giant cells (Fig 836) This lesion probably is related to chondroblastoma. Curettement is curative.

Glomus tumor has been reported in a terminal phalanx (Lattes) The *neurilemoma* has been seen in the humerus by Gross, and in the femur by Hart. We

have seen a *lipoma* of the rib with cortical bone destruction Dickson has reported a case of *intramedullary lipoma* Dawson has reported an authentic case of *liposarcoma* of bone The so-called *adamantinoma* occurs predominantly in the tibia but rarely may occur in other long bones such as the femur, ulna, and fibula (Baker) This lesion produces a slowly growing destructive process in the shaft or metaphyseal area of the tibia Microscopically it shows variable patterns. It may be highly vascular, resemble a basal cell carcinoma or an adamantinoma. It is best treated by amputation for local recrudescence and even distant metastases may appear

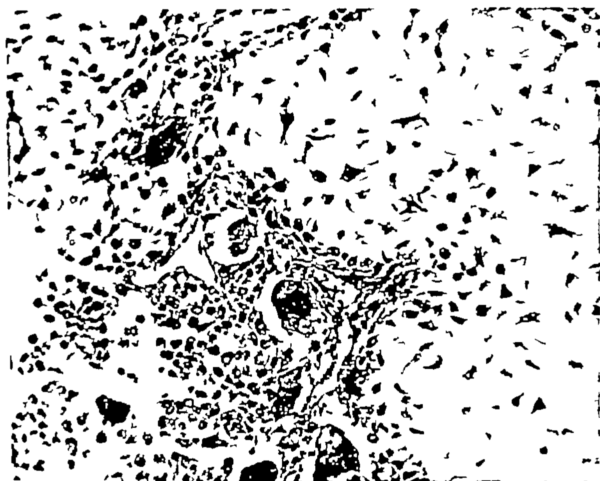


Fig 836—Photomicrograph of chondromyxoid fibroma with giant cells cartilage and cellular zones. (×200) (W U neg 54-1345)

MALIGNANT TUMORS

Laboratory Findings

The only specific test of value in the diagnosis of bone tumors is the acid phosphatase. Elevation of this enzyme in serum is usually evidence of metastatic carcinoma arising from the prostate (a rare exception is infarction of the prostate) Elevation of the alkaline phosphatase is merely an expression of bone production and is nonspecific. It can be elevated in bone producing lesions such as osteosarcoma, hyperparathyroidism, Paget's disease, and metastatic carcinoma of the

breast or prostate The alkaline phosphatase is normal in many processes which predominantly destroy bone such as osteolytic osteosarcoma, metastatic carcinoma from the kidney and plasma cell myeloma. Plasma cell myeloma is practically the only tumor in which there are other laboratory findings that lend weight to the diagnosis However these findings occur only when the process is disseminated. With a localized lesion of bone all laboratory findings, including bone marrow are usually normal In disseminated multiple myeloma the serum protein frequently is elevated (as high as 20 Gm per cent), this elevation involves mainly the globulin fraction. The electrophoretic pattern of the serum proteins may be diagnostic, but in certain instances of apparently localized plasma cell myeloma it is normal. Bence Jones protein is present in about half the cases. Serum calcium and phosphorus also may be elevated because bone is being destroyed so fast that the kidneys do not have time to excrete it. The uric acid may be increased through catabolism of nucleoproteins derived from myeloma cells (Stewart) Elevation of the sedimentation rate may be the first evidence of recurrence of Ewing's tumor

Biopsy: Incisional, Aspiration, Frozen Section

The therapy of malignant tumors often implies amputation in a young person. Before such a procedure it is imperative that the pathologic diagnosis be correct. The surgeon must obtain adequate material for pathologic diagnosis even though *the lesion is confined entirely within the bone If possible he should excise a segment of bone including both the involved and uninvolved areas.* He should curette material from the marrow cavity only when frozen section of the initial incisional biopsy is not diagnostic. The operator should avoid excessive trauma to the tumor while securing a biopsy and should so place the biopsy incision that it may be entirely removed if subsequent radical operation is indicated. The use of a tourniquet proximal to bone lesions in the extremities while securing the biopsy theoretically may reduce the possibility of distant spread. *If there is any question of infection this material must be properly studied bacteriologically*

Aspiration biopsy of bone tumors has been performed extensively at the Memorial Hospital Snyder reported 385 cases of which 67.5 per cent were definitely and specifically diagnostic. In no case did a false aspiration diagnosis lead to amputation for a benign process We feel that aspiration biopsy after preparation of paraffin sections is similar to a small biopsy and is particularly valuable in lesions which are deeply located (Sirsat)

Frozen section diagnosis may be difficult. However certain bone tumors such as Ewing's sarcoma osteosarcoma, and chondrosarcoma may extend beyond the bone and form soft tissue masses On several occasions frozen section diagnosis has given unexpected results. An osteolytic lesion of the pelvis was thought to be a primary malignant bone tumor and hemipelvectomy was contemplated. Frozen section demonstrated metastatic carcinoma. An osteolytic lesion of the femur with extension into the soft tissue was considered Ewing's tumor but proved to be *eosinophilic granuloma. At times an exact diagnosis cannot be made* but the pathologist can usually say whether the lesion is benign or malignant. Frozen

section of a lesion of the epiphysis showed well-differentiated cells and a few giant cells. A diagnosis of benign lesion was made, curettement was done and a diagnosis of chondroblastoma was made on the permanent sections

Osteosarcoma

Osteosarcoma is the commonest primary malignant bone tumor It usually occurs in patients between 10 and 25 years of age being slightly more frequent in males Another peak age incidence occurs after 40 Most of the patients are males whose tumors are superimposed on Paget s disease. Multiple osteosarcomas can occur in Paget s disease There are also rare cases in which multiple foci of



Fig 837 —Roentgenogram of an osteosarcoma of the upper end of the femur associated with fracture and Paget s disease. (W U neg 48-6536)

Fig 838 —Gross photograph of the tumor shown in Fig 837 at the point of fracture demonstrating extension of the hemorrhagic neoplasm up the shaft and out into the soft tissues. Note porous thickened cortical bone of Paget s disease. (W U neg 48-5008)

origin appear without antecedent Paget s disease (Silverman) Osteosarcoma may follow poorly planned irradiation therapy (Cahan has reported 11 cases and Hatcher 27) Martland reported the development of osteosarcoma in factory workers who moistened their brushes in their mouths while applying radium paint to luminous figures on watches. Trauma as far as is known does not cause bone tumor if it did one would expect to find them arising after the trauma of various orthopedic procedures bullet wounds or severe injuries Trauma usually only calls attention to an already present advanced bone tumor

These highly malignant osteosarcomas develop for the most part in the metaphyseal area of the long bones particularly the lower end of the femur the upper

end of the tibia, and the upper end of the humerus They also develop in the pelvic bones, the upper end of the femur, the mandible and the fibula or are superimposed on Paget s disease in long bones, vertebra or skull (Figs. 837 and 838) Grossly these tumors vary in vascularity cartilage and osseous content. As





Fig 839 —Roentgenogram of osteosarcoma of the upper end of the femur demonstrating prominent periosteal bone proliferation. (W U neg 48-6537)

Fig 840 —Gross photograph of the tumor shown in Fig 839 demonstrating elevation of the periosteal growth in the metaphyseal and diaphyseal areas. (W U neg 48-5884)

they grow they extend along the marrow cavity and elevate or perforate the periosteum. If they elevate the periosteum, they may produce the radiographic picture designated as Codman s triangle (a nonspecific finding) This angle is formed by the elevated periosteum and the underlying bone (Figs. 839 and 840) If the epiphysis is closed the tumor may extend throughout the entire epiphysis. Rarely following fractures or extension through the periosteum, they break into the joint. They practically never ulcerate through the skin or involve regional lymph nodes. In a rather wide experience we have seen involvement of lymph nodes in only two

instances once in a hilar lymph node in a disseminated osteosarcoma and once in a cervical lymph node from an osteosarcoma of the mandible. They usually metastasize through the blood stream to distant sites, the lung being most common

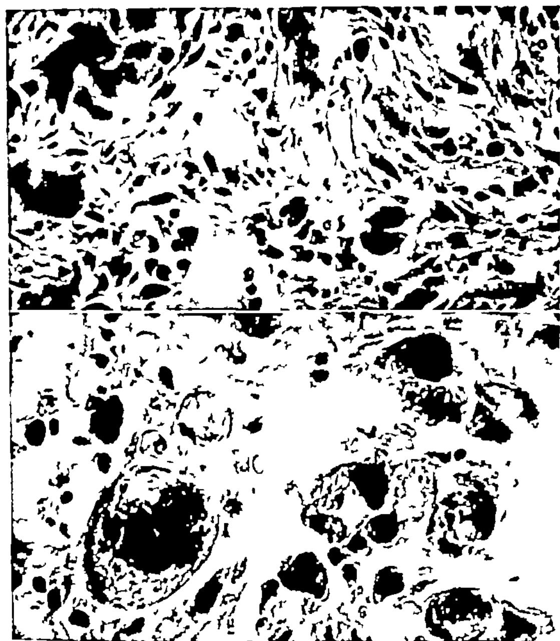


Fig. 841 —Photomicrograph of an osteosarcoma producing large amounts of neoplastic osteoid and sarcomatous stroma. (High power)

Fig 842 —Photomicrograph of osteosarcoma with bizarre tumor giant cells. (×600) (W U neg. 52-4081)

Microscopically the tumor may exhibit changes ranging from extremely well-differentiated tissue to highly anaplastic lesions (Figs. 841 and 842) Biopsy of an undifferentiated osteosarcoma may show a highly vascular lesion with tumor cells of greatly variable size and shape growing between and lining blood vessels without evidence of osteoid formation

By contrast a tumor may produce in a disorderly fashion well-differentiated bone and large amounts of osteoid (Fig 841) Wide areas of neoplastic cartilage occur in some tumors. In the easily recognized osteosarcoma there is sarcomatous stroma and immature osteoid recognized by its faint eosinophilic and glassy appearance. The lesions mistaken for osteosarcoma include any in which there is rapid bone growth We have seen slides of exuberant callus formation misdiagnosed by examining them without knowledge of an antecedent fracture. On several occasions the highly proliferative lesion of soft tissue designated as myositis ossificans has been diagnosed by competent authorities as osteosarcoma. Lichtenstein has cited an instance of gumma of bone which was diagnosed incorrectly as osteosarcoma.

The prognosis for patients with osteosarcoma is not as dismal as many believe. If the pathologic diagnosis is restricted to osteosarcoma excluding such lesions as chondrosarcoma, fibrosarcoma periosteal sarcoma and osteogenic sarcoma of the jaw the five year survival approaches 20 per cent (Coventry)

Parosteal (juxtacortical) osteogenic sarcoma is an infrequent primary slowly growing malignant tumor of bone. It arises in a juxtacortical position in the metaphyses of long bones and may have a life history of 10 to 15 years It forms a large lobulated mass and has a tendency to encircle the bone. The diagnosis is suggested by the roentgenographic picture. If a biopsy is taken of the soft tissue extension of the tumor it will show a disorderly pattern of well formed bone, osteoid, and an abnormal stromal pattern. This lesion has to be differentiated from myositis ossificans which has an orderly pattern of bone formation without a sarcomatous stroma. With adequate treatment the prognosis is excellent (Dwinnell)

Chondrosarcoma, Osteochondroma Enchondroma

Chondrosarcoma must be separated from osteosarcoma not only because of distinctive growth and microscopic differences but because of the relatively good patient prognosis. Chondrosarcomas may arise from the cartilaginous cap of an osteochondroma. The origin of this tumor from an enchondroma is exceedingly rare. A cartilaginous tumor present in a long bone is almost invariably a chondrosarcoma. In Dahlin's 212 cases of chondrosarcoma, 19 apparently arose from osteochondroma, but not a single case appeared to arise from an enchondroma.

The *osteochondroma* is the commonest benign bone tumor In 40 cases studied at Washington University the average age of the patient at onset was 10.9 years in 36 cases the tumor appeared before the patients were 20 years old. The average greatest dimension was 3 7 cm. and the largest tumor measured 8.5 cm. Smaller tumors were sessile and the larger ones were pedunculated. All had a cap of cartilage covered by a fibrous membrane continuous with the periosteum of the adjacent bone The average thickness of the cartilage cap was 0 6 cm. (0 1 to 3 0 cm.) in only 7 cases was the cap thicker than 1 cm. The cartilaginous cap tended to be lobulated in large tumors (Fig 843) The gross and microscopic appearance of a single lesion of multiple cartilaginous exostoses (Ehren

fried's hereditary deforming chondrodysplasia diaphyseal aclasis [Fairbanks]) cannot be distinguished from osteochondroma

Benign enchondromas most frequently occur in the small bones of the hands and feet they expand and thin the cortex and may be multiple Enchondromas of the long bones, which are rare in our experience, produce a sharply delimited radiolucent lesion without cortical expansion or thinning Small areas of calcification may occur within the tumor Multiple enchondromas (Ollier's disease) occur often with a unilateral distribution This rare disease is better designated as skeletal enchondromatosis.

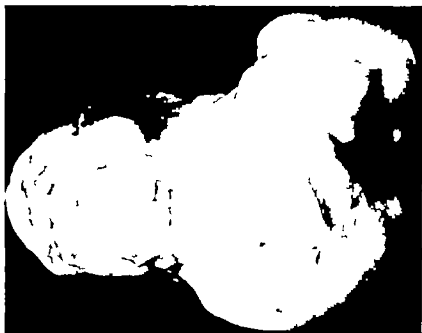


Fig 843 —Gross photograph of a large osteochondroma with a lobulated cartilaginous cap (W U neg 51 3690)

Chondrosarcomas arise from the cartilaginous cap of osteochondromas. The signs of malignant change in an osteochondroma include increased growth after the age of 20 rapid growth during adolescence the presence of a large tumor (over 8 cm.) and a thick cartilaginous cap Fortunately only a small proportion of osteochondromas the commonest benign bone tumor undergo malignant change (less than 5 per cent) The thickest cap of benign osteochondroma seen in the Barnes Hospital was 3 cm but the average was only 0 6 cm. However our peripheral chondrosarcomas had cartilaginous caps nearly always over 3 cm. thick the thinnest one was 2 cm. The greatest dimension varied from 8 to 25 cm. in 25 peripheral chondrosarcomas (Fig 844) There is a greater chance of malignant change occurring in multiple cartilaginous exostoses. Chondrosarcoma occurred in 3 of Jaffe's 28 cases and in 3 of our 7 cases The longer such cases are followed the greater will be the number developing this malignant tumor Some may develop more than one chondrosarcoma Central chondrosarcomas usually arise de novo rather than from enchondromas The enchondromas of the hands and feet with the exception of the os calcis practically never undergo malignant

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change (Lansche) Chondrosarcomas of long bones rapidly penetrate the cortex and involve the adjacent soft tissues. Also a strong probability of malignant transformation exists in one or more of the cartilaginous lesions of skeletal enchondromatosis.

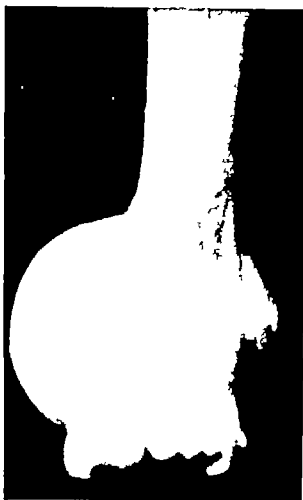


Fig 844—Clinical photograph of a large peripheral chondrosarcoma of the os calcis in a 36-year-old man. This tumor was of long duration the patient finally came to the clinic because he could no longer put on his shoe.

Radiographically peripheral chondrosarcomas are large, often with splotchy calcification and at times have a bony base (Figs. 845 and 846) These tumors arise from the bones of the pelvis, the upper end of the femur the upper end of the humerus and from rarer locations such as the os calcis or vertebrae. Chondrosarcomas within the long bones break through the cortex, do not grow as large as the peripheral type, but also contain spotty calcification (Figs. 847 and 848) The diagnosis of well-differentiated chondrosarcoma may not be made for such reasons as a long history of growth, lack of follow up and the failure of the pathologist to recognize the subtle microscopic changes which indicate a malignant cartilaginous tumor

The microscopic diagnosis of chondrosarcoma rests on the identification of abnormal nuclei in cartilage cells The nuclei are plump atypical, and at times

multinucleated (Figs. 819 and 850) Areas near the growing edge are particularly diagnostic Microscopically an incorrect diagnosis of chondrosarcoma can be made particularly in the enchondromas of the small bones of the hands and feet where cellularity may be prominent Frequently the statement is made that a



Fig 845.—Roentgenogram of a typical chondrosarcoma of the ilium showing splotchy calcification. (W U neg 49 5363)

Fig 846.—Gross photograph of the tumor shown in Fig 845 following hemipelvectomy This was a well-differentiated chondrosarcoma. The patient has now lived nine years without recurrence (W U neg 49 5172)

benign tumor became malignant or that a benign tumor recurred We have had the opportunity of examining tissue on two or more occasions over periods of five months to twelve years from 16 patients subjected to repeated operations for recurrences *In none of these was the initial tumor clearly benign* We believe therefore that in these instances the pathologist incorrectly diagnosed the initial tumor There is good correlation between poor differentiation rapid growth rate, and metastases. The poorly differentiated tumors and those with mitoses metastasize early usually to the lungs. Blood stream invasion is particularly common we have seen lymph node metastases (axillary) on only one occasion.



Fig 847 —Roentgenogram of a chondrosarcoma of the upper end of the femur It had broken through the cortex. (W U neg 49-4395)

Fig 848.—Gross photograph of the tumor shown in Fig 847 demonstrating replacement of the medullary cavity and cortical destruction. (W U neg 49-4323)

Fig 849 —Photomicrograph of the lesion showing scattered tumor cells with plump atypical nuclei. This was a difficult diagnosis to make but it was thought to be unequivocal. (High power) (W U neg 50-2301)

Fig 850 —Photomicrograph of undifferentiated metastases in the lung superficially resembling fibrosarcoma. The patient had widespread pulmonary metastases at autopsy (High power) (W U neg. 50-2302.)

Inset Photomicrograph of a chondrosarcoma demonstrating plump atypical nuclei (High power) (W U neg. 48-6691)

Clinicopathologic Correlation.—The clinician and pathologist must remember that practically all cartilaginous tumors within long bones and ribs are malignant and that cartilaginous tumors of the hands and feet are benign. If cartilaginous tumor begins to grow rapidly after adolescence and reaches the size of 8 cm. or more, it is invariably malignant. If this tumor is biopsied implantation is likely, therefore, if a large cartilaginous tumor is so located that the biopsy site cannot be entirely excised, the initial surgery should be radical. If an extremely large tumor involves the pelvic bone wide block excision or even hemipelvectomy is indicated without prior histologic diagnosis. About ninety per cent of the patients cured by hemipelvectomy had the operation for chondrosarcoma (O'Neal and Ackerman).

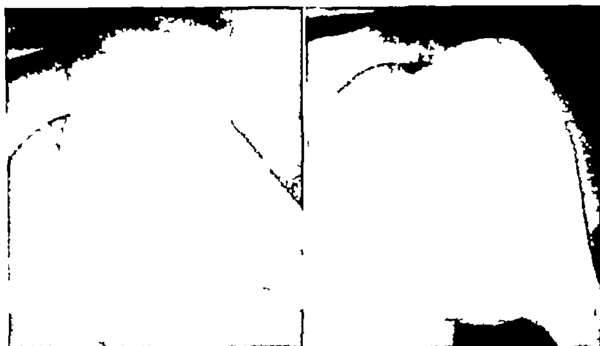


Fig. 851.—Roentgenograms of a giant cell tumor of the upper end of the humerus in a girl 20 years of age who refused treatment. There was an interval of nineteen months between x rays. (W U negs. 48-6970 and 48-6971.)

Giant Cell Tumor (Benign and Malignant)

This tumor is being discussed with malignant bone tumors because occasionally it is malignant (about 25 per cent of cases). Giant cell tumors of bone are rare in patients under 20 years of age (Jaffe). The youngest patient we have seen with a giant cell tumor was 14 years of age. They occur more frequently in women than in men. They arise most commonly from epiphyseal areas of long bones in the following order of frequency: the lower end of the femur, the upper end of the tibia and the lower end of the radius. They appear in many other bones however including the patella, fibula and humerus. Only rarely do they occur in metacarpal and metatarsal bones. We have seen only one in a phalanx. This tumor grows rather slowly and gradually spreads into the metaphyseal area (Murphy) (Fig. 851). We do not agree with Willis that this tumor ever arises as a cartilaginous variant from the metaphyseal zone. It thins the cortex of the

bone but only rarely produces periosteal bone formation. These tumors may break through the cortex invade intermuscular septa, or even cross a joint space (Windeyer) On section the tumor contains loculated spaces transversed by fibrous trabeculae areas of hemorrhage are common within it (Fig 852) These tumors may be small or large. If they become large in long bones fractures may complicate the pathologic picture.

X ray examinations often show changes purported to be diagnostic. However we have seen lesions diagnosed as giant cell tumors which proved to be a single focus of plasma cell tumor fibrosarcoma, or chondrosarcoma. Whether a giant cell tumor is benign or malignant cannot be determined radiographically



Fig 852.—Gross photograph of a benign giant cell tumor of the tibia. It has thinned the cortex of the bone. It was resected because of a radiographic diagnosis of malignant giant cell tumor but proved to be entirely benign. (W U neg. 49-2379)

Microscopically the giant cell tumor is made up of two components stromal cells and giant cells. The giant cells often are large and frequently have many nuclei (twenty or thirty are usual) which frequently occupy the center of the cell. The prominence of the giant cells gives the tumor its name The microscopic evaluation of a given giant cell tumor depends on careful study of the stromal cells. In the obvious malignant tumor the stroma shows increased cellularity and mitotic activity It is imperative that several sections of curettings be examined We have had a giant cell tumor in which the original sections of the curettings showed no malignant tumor but in time this tumor recurred, invaded the soft tissue, and metastasized to the lungs as a fibrosarcoma. Only two sections had been made of the initial curettings further sections of them showed malignant tumor in the primary lesion (Figs. 853-856) Unfortunately this lesion may rarely appear to be entirely benign pathologically yet metastasize and kill the patient The metastases in these instances may also appear histologically benign. Such cases limit the value of grading

Many benign pathologic lesions with giant cells have been called giant cell tumors. These lesions include such diverse entities as metaphyseal fibrous defect,

chondromyxoid fibroma chondroblastoma eosinophilic granuloma, unicameral bone cyst osteitis fibrosa cystica of hyperparathyroidism aneurysmal bone cyst, and osteoid osteoma. So-called giant cell tumors of tendon sheath are not related to giant cell tumors of bone One or more giant cells in a bone lesion do not justify

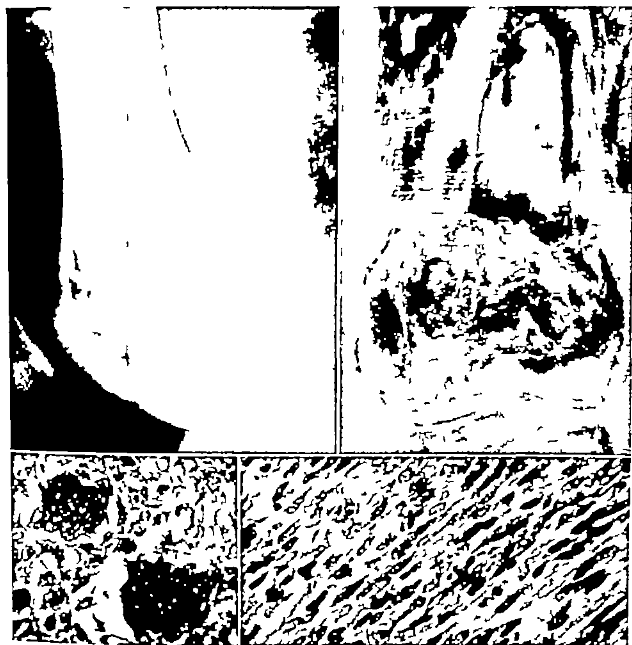


Fig 853 —Roentgenogram of a giant cell tumor of the distal end of the femur The lesion was curetted and replaced with bone chips. (W U neg 49-5963)

Fig 854 —The giant cell tumor recurred, necessitating amputation. The gross specimen demonstrates the bone chips still in place with tumor replacing the femur Review of the original sections showed benign giant cell tumor but recuts of curetted material demonstrated a malignant stroma (W U neg 50-663)

Fig 855 —Photomicrograph of the original sections of the curettings show areas of rather innocuous-appearing stroma with typical multinucleated giant cells. These changes were called benign. (High power) (W U neg 51 1535)

Fig 856.—Photomicrograph of this malignant giant cell tumor which has the appearance of a fibrosarcoma. There was no evidence of osteoid formation. The patient died of pulmonary metastases. (×460) (W U neg 50-3550)

a diagnosis of giant cell tumor any more than a few giant cells of the Langhans type justify a diagnosis of tuberculosis The inclusion of the above entities has been responsible for the high cure rates reported in the past.

The vascularized fibrous framework is the most important part of this tumor it is believed that the giant cells result from fusion of nuclei of stromal cells. We and many others think that giant cell tumors arise from undifferentiated supporting connective tissue of the marrow Willis and many of the English school believe that these tumors arise from osteoclasts and should be designated as osteoclastomas. If a giant cell tumor occurs in the maxilla, mandible or in some atypical location such as the small bones of the hand a parathyroid adenoma must be suspected. We have seen 3 patients with functioning parathyroid adenomas seek medical care initially for giant cell tumors in the small bones of the fingers.

There is no doubt that a giant cell tumor eventually may become malignant or that some are malignant at initial biopsy The exact frequency of malignant change in giant cell tumors is relatively high Murphy reported 5 of 31 as malignant. Dahlin also reported 11 of 120 as malignant. At least one third of these tumors recur after treatment. We have seen operative transplantation of the tumor into the adjoining soft tissues (Joynt)

Obviously no giant cell tumor should be treated without thorough study of biopsied material In certain areas where deformity does not result, resection will prove effective. Many orthopedic surgeons advocate curettement with zinc chloride cauterization and replacement with bone chips. We doubt the value of cauterization. Well planned irradiation therapy for giant cell tumors of bone may be effective. However the results reported in the literature often are difficult to evaluate because many of the lesions were not biopsied were in unusual locations and occurred in children

Fibrosarcoma

Fibrosarcoma of bone is a specific neoplasm arising in the metaphyseal area of long bones. Approximately 50 per cent of these occur in the distal femur or proximal tibia (McLeod) It destroys the cortex, is osteolytic, and often extends into the soft tissues. In our experience fibrosarcoma practically never arises from the periosteum. The diagnosis of this specific tumor is seldom made radiographically only a diagnosis of malignant bone neoplasm is suggested. Microscopically this tumor is a fibroblastic neoplasm similar to soft tissue fibrosarcomas (Figs. 857 and 858) This tumor is distinct from other bone tumors We have seen examples in which innumerable sections of the primary tumor and its metastases showed no osteoid formation. These tumors must be treated radically The rare tumors arising from periosteum have an excellent prognosis only 1 of 13 metastasized (Stout)

Ewing's Tumor

Ewing's tumor of bone occurs in children and adults under the age of 30 most cases occur in patients aged 10 to 20 This tumor occurs most commonly in the long bones (femur tibia humerus and ulna) and infrequently in the bones of



Fig 857 —Gross photograph of fibrosarcoma of the tibia This lesion produced an osteolytic defect and was confused radiographically with giant cell tumor (W U neg 57 789)



Fig 858 —Photomicrograph of a fibrosarcoma Note the spindle-shaped cells. There was no evidence of osteoid formation in many sections. (×400) (W U neg 49 5369)

the pelvis rib, vertebra, mandible and clavicle. It arises in the medullary canal of the shaft The first radiographic changes are cortical thickening and widening of the medullary canal With progress of the lesion reactive periosteal bone may be deposited in layers parallel to the cortex (onionskin appearance) or at right angles to it (Fig 859) It does not produce a diagnostic radiographic appearance (Swenson)

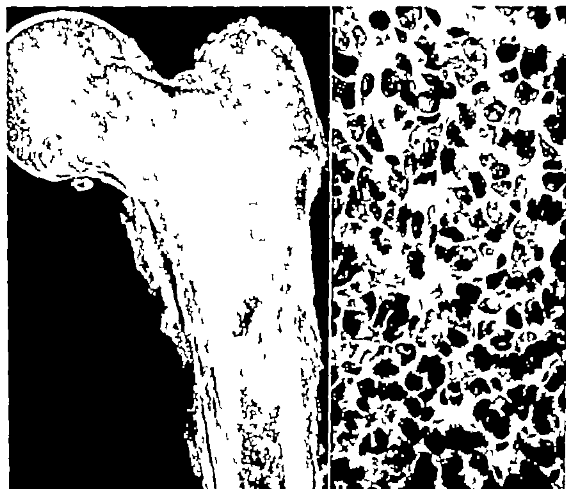


Fig 859 —Gross photograph of resected end of the femur involved by Ewing's sarcoma. Note complete replacement of the marrow cavity and prominent cortical thickening microscopically destruction and invasion of the epiphysis were present. (W U neg 50-1409)

Fig 860 —Photomicrograph of a Ewing's sarcoma with uniform cells, inconspicuous cytoplasm, and no osteoid. (×600) (W U neg 51 294)

Microscopically Ewing's tumor consists of solid sheets of cells which appear to arise from young reticular cells of the bone marrow Individual cells are uniform with poorly defined nucleoli and inconspicuous cytoplasmic outlines (Fig 860) The tumor is fairly well vascularized it often contains cellular areas with necrosis, and the tumor cells may be grouped around blood vessels producing a false rosette. This tumor does not form reticulin or osteoid

Willis has correctly pointed out that metastatic neuroblastoma may easily be confused with primary Ewing's tumor both roentgenographically and microscopically

Growth in tissue culture is diagnostic of neuroblastoma because neurites quickly grow out in twenty four to forty-eight hours. The poorly differentiated neuroblastoma cannot be differentiated microscopically However patients with well authenticated microscopically *proved* Ewing's tumor have survived five or more years after irradiation or operation This tumor is often confused with undifferentiated carcinoma lymphosarcoma, or even eosinophilic granuloma

Clinically Ewing's sarcoma in a young adult may simulate osteomyelitis because of the pain disability, fever, and leukocytosis. The lesion is highly radiosensitive but practically never radiocurable. Dissemination occurs quickly to lungs and other bones, particularly those of the skull. Unfortunately involvement may be multifocal There is a certain parallelism between this tumor and plasma cell myeloma.

Reticulum Cell Sarcoma

Reticulum cell sarcoma of bone is a definite entity About 60 per cent of the patients are over 30 years old although the tumors do occur in younger persons. The sex distribution is about equal

Grossly this tumor involves the shaft of the bone, producing cortical and medullary destruction The destruction within the bone is patchy, with minimal to moderate periosteal reaction usually of the lamellated type. The tumor is pinkish gray and granular and it frequently extends into the soft tissues and invades the muscle. Sherman believes that the radiographic patterns may be extremely helpful in diagnosis. A combination of bone production and bone destruction often involves a wide area of a long bone (Fig 861) Lichtenstein has seen involvement of a joint cavity Although Sherman may be able to make this diagnosis roentgenographically because of his wide experience most of our cases have been diagnosed as osteosarcoma or chronic osteomyelitis.

Microscopically reticulum cell sarcoma must be distinguished from Ewing's tumor Reticulum cell sarcoma has larger reticulum like cells and may exhibit phagocytosis Cell nuclei usually have prominent nucleoli, unlike the fine nucleoli of Ewing's sarcoma (Fig 862) Cytoplasmic outlines of reticulum cell sarcoma are well defined cytoplasm is often eosinophilic. The cellular outlines of Ewing's tumor are indistinct. Reticulin is between individual cells and groups of cells in reticulum cell sarcoma. Ewing's tumor shows little or no reticulin.

The importance of making this diagnosis rests with the fact that the neoplasm is often curable by well planned radiotherapy and/or surgery In 28 patients followed for over five years and treated by a variety of methods, ten were apparently cured (36 per cent) (Ivins)

Plasma Cell Tumor

The pathologic expressions of plasma cell tumors are diverse. Disseminated myeloma is the most common clinically It occurs slightly more often in males than in females and between 40 and 60 years of age, rarely occurring before 30 The tumor when disseminated, produces osteolytic lesions in the skull, ribs vertebrae and flat bones. Under these circumstances the life expectancy is usually under two years.

Plasma cell tumors may first appear clinically in the soft tissue The most common location is nasopharyngeal. We have seen it in such areas as mediastinum, skin, and lymph nodes Rarely (about 35 cases reported) plasma cell tumors occur with the clinical and hematologic manifestations of a leukemia (Moss) Almost all lesions initially of soft tissue eventually become disseminated in bone. Christopherson collected all the apparently localized cases of plasma cell tumors only 5 of the entire group still had localized disease after ten years follow up Of the 92 tumors reported by Carson only 1 could be considered a possible localized tumor

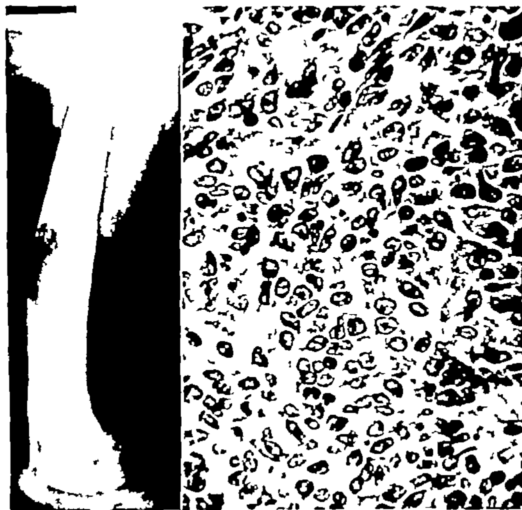


Fig. 861 —Roentgenogram of reticulum cell sarcoma involving the lower end of the femur demonstrating bone destruction and bone production. Such lesions are often erroneously diagnosed as chronic osteomyelitis. (W U neg 49-4628.)

Fig 862.—Photomicrograph of reticulum cell sarcoma of bone Note the large cells with prominent nucleoli. Reticulin is present. (×600) (W U neg 50-3840.)

An advanced plasma cell tumor often fractures. The tissue is hemorrhagic and cellular (Fig 863) The focal slowly growing tumor may have a fairly well-defined border is grayish yellow homogeneous and firm. Microscopically an obvious well-differentiated plasma cell tumor grows in sheets separated by fine trabeculae which are seen well by reticulin stain These plasma cell tumors prob-



Fig 863 —Roentgenogram of an osteolytic lesion of the upper end of the tibia due to a localized lesion of plasma cell myeloma. Such a lesion has the osteolytic appearance of metastatic carcinoma. (W U neg 50-417)

Fig 864 —Photomicrograph of a well-differentiated plasma cell tumor showing plasma cells with eccentric nuclei and characteristic arrangement of the chromatin (High power) (W U neg 50-228)

Fig 865 —Photomicrograph of a highly undifferentiated plasma cell tumor with tumor giant cells. (×600) (W U neg 50 3724)

ably arise from reticulin cells. We agree with Lichtenstein that myeloma should not be divided into subvarieties (plasma, myeloid, erythroid, and lymphoid), and that the neoplasm has a single cell type which may vary but is called the myeloma cell. Plasma cells are commonly found in chronic inflammatory conditions. They *are particularly common within the oral cavity The mere presence of large num*bers of plasma cells should not be diagnosed as plasma cell tumor The plasma cells of a granulomatous process are well differentiated and often contain Russell bodies (aggregates of eosinophilic material in the cytoplasm) Other chronic inflammatory cells will be interspersed between the abundant plasma cells. Such plasma cell granulomas may become large enough to be mistaken for a true neoplasm. Certainly the lesions of the conjunctiva are granulomas and we have seen other granulomas in the oral cavity mediastinum, lung stomach, kidney testis, and bone The importance of the differentiation of this granuloma from plasma cell myeloma is obvious Plasma cell tumors may be highly undifferentiated and difficult to identify they may even have the pattern of reticulum cell sarcoma (Figs. 864 and 865) However careful examination of many fields invariably reveals small zones of recognizable plasma cells. The well-differentiated plasma cell has an eccentric nucleus a cartwheel arrangement of the chromatin and often two nuclei The perinuclear halo often mentioned is not conspicuous.

The laboratory findings are often diagnostic of the disseminated type of plasma cell myeloma of bone Thorough study of a patient with an apparently single lesion of bone often demonstrates it to be only a localized manifestation of a disseminated process. Such study may show other lesions in bone. Trephine biopsy of the sternal marrow is particularly important, for it may show increased plasma cells in the marrow This finding often is present in the face of an otherwise negative skeletal series, normal serum proteins, normal electrophoretic pattern of serum proteins and absence of Bence Jones protein. Long time follow up, particularly of all localized lesions, is mandatory The case illustrated in Fig 863 had a local lesion treated and sterilized by irradiation and the defect replaced by bone chips. At that time all laboratory and x ray examinations were normal except for slight elevation of the plasma cells in the sternal marrow The patient was still working eight years later but had disseminated disease evidenced by massive replacement of the sternal marrow by plasma cells. This patient illustrates the effectiveness of irradiation therapy in controlling localized lesions, and that patients with myeloma may live well over five years.

Patients with disseminated multiple myeloma due to extensive involvement of the vertebrae and ribs develop a typical hunchback deformity Rib fractures *are common anemia is prominent and death occurs rather quickly* Death occurred in 57 of 60 patients with disseminated myeloma in the first two years. Thirty-one of these patients died within 3 months of initial diagnosis (Carson) Irradiation therapy may sterilize or operation may eradicate localized lesions of bone X ray therapy or urethan occasionally gives striking palliation.

Metastatic Tumors

The incidence of osseous metastases varies with the primary neoplasm and the thoroughness of postmortem examination We are concerned chiefly with those

metastatic lesions which may be confused clinically with primary benign or malignant bone lesions In most instances of bone metastases the primary tumor is known Excluding these metastatic tumors are still the commonest of all malignant bone neoplasms. These lesions may be osteolytic, osteoblastic, or both The bone or bones involved and the character of the changes seen radiographically are helpful in predicting the primary neoplasm. Certain occult primary carcinomas (carcinoma of the thyroid and kidney) may develop only a single bone metastasis



Fig 866—Roentgenogram of a metastatic adenocarcinoma involving the shaft of the femur producing prominent periosteal bone proliferation. (W U neg 52 3151)

Fig 867—Photomicrograph of tumor cells forming acini growing between dense bone trabeculae (×200) (W U neg 52 3456) (X ray and slide contributed by Dr P K. Lund, Seattle Wash)

Both of these tumors may manifest single bone metastases many years after removal of the primary neoplasm. Thyroid carcinoma commonly metastasizes to the bones of the shoulder girdle, skull, ribs and sternum. Carcinoma of the kidney may involve the skull sternum, flat bones of the pelvis, and upper end of the femur They both produce osteolytic defects if the tumor extends through the bone into soft tissue, pulsating masses may be present. Carcinomas of almost every organ may produce an apparent single metastasis to bone The area in

volved in the long bones is the metaphyseal region. It is often stated that metastases do not occur below the knees or elbows. However numerous exceptions occur. We have seen metastatic epidermoid carcinoma of the lung in a terminal phalanx carcinoma of the breast in the small bones of the feet and carcinoma of the cervix appearing as a poorly defined cyst in the lower end of the tibia. Periosteal bone proliferation may accompany a metastatic lesion. This is likely to occur in certain sclerosing metastatic lesions such as those of the prostate however these metastases are usually multiple and often in ribs. We have seen a single metastasis in a long bone produce excessive periosteal proliferation simulating primary osteosarcoma. Such changes are unusual but have occurred in metastatic rectal and pancreatic carcinoma (Figs. 866 and 867)

It is imperative that such metastatic lesions be biopsied in order to avoid treatment designed for primary malignant bone tumors. Once a biopsy is available, the microscopic recognition usually is simple the source of the bone metastasis may be suggested microscopically particularly in carcinoma of the kidney thyroid and large bowel. If the tumor is squamous carcinoma in a thoracic vertebra and the patient is a male in the sixth decade metastatic carcinoma of the lung is likely

Sarcomas of soft tissue origin do not frequently involve bone except by direct invasion. Hodgkin's disease frequently involves bone when the disease is advanced. Lymphosarcomas may produce a bone defect, usually osteolytic, but invariably the lymphosarcoma has been previously noted and diagnosed.

Most metastatic bone lesions cause pain. Treatment is for its relief. Irradiation therapy of localized lesions is the treatment of choice. Disseminated metastases from carcinoma of the prostate may be palliated by the use of estrogen therapy and/or orchiectomy. The pain of metastatic carcinoma from the breast is commonly relieved by testosterone. Occasionally striking objective improvement in the condition of the bone is obtained. Other types of hormonal therapy than testosterone are thought less effective in the palliation of generalized bone metastases. In a few rare instances a single metastatic focus, particularly from the thyroid and kidney may be excised with benefit.

MISCELLANEOUS CONDITIONS

Paget's Disease

Paget's disease occurs in about 90 per cent of instances in persons over 55 years of age. It is rare before the age of 40 and uncommon between the ages of 40 and 55. The disease affects men slightly more commonly than women (4 to 3). Collins reported that about 1 of every 30 patients over the age of 40 had Paget's disease in one of several locations at autopsy. The most common sites are the lumbosacral spine, pelvis, and the skull. It may occur in the femur tibia, or fibula, but is extremely rare in the ribs. The process may involve only a portion of a single bone. Initially this lesion is osteoclastic. Abnormal hyperplasia soon follows as evidenced by primitive coarse fibered bone in discontinuous trabeculae. Later massive, thick trabeculae with disjointed lamellar patterns occur. Reticulin stains are often very helpful in studying the pattern of growth. The use of polarized

light is less instructive When lamellar bone becomes organized a mosaic of cement lines appears. This is caused by the abrupt interruptions and changes in direction of bone lamellae and fibers resulting from resorption and regeneration of masses of bone during the course of the disease These lines are outlined clearly by Ehrlich's acid hematoxylin Collins also stressed the fact that the incidence of superimposed osteosarcoma is quite low if one considers the frequency of Paget's disease The complications of fracture and sarcoma in Paget's disease however represent a significant number of clinical problems because of the commonness of the disease

Rarely Paget's disease is predominantly a monostotic process in a long bone (Seaman) We have seen it in an apparent monostotic phase in the maxilla the mandible and in a collapsed vertebra Under these conditions the alkaline phosphatase may be normal (Figs 868 and 869) The key to the microscopic pattern of the disease is the mosaic of numerous and scalloped cement lines (Schmorl) There are many pathologic processes which undergo active reparative change accompanied by new bone formation with cement lines If careful attention is paid to the pattern of these normal cement lines which are orderly and structurally well oriented, these processes will not be confused with the microscopic appearance of Paget's disease. These lesions include irradiation effect chronic osteomyelitis, reactive bone surrounding metastatic cancer and polyostotic fibrous dysplasia. Uehlinger points out that eccentric atrophy of the cortical bone is invariably present in polyostotic fibrous dysplasia but absent in Paget's disease. Rapid dissolution of bone substance may occur if a patient with Paget's disease of a long bone is immobilized because of fracture (Reifenstein)

Myositis Ossificans

Myositis ossificans is a poor name for a group of conditions that are often mistaken microscopically for osteosarcoma. This is a poor name because this lesion often does not involve muscle have inflammation or form bone About one-half the cases have no history of trauma Unfortunately this condition may arise in such atypical sites as the buttock. If found early in its evolution or in an atypical location its biopsy diagnosis is difficult Its distribution is indicated by the following statement

> Strauss statistics dealing with 127 cases of traumatic myositis ossificans show the following anatomic distribution sixty four of these occurred in the flexor muscles of the upper arm the brachialis anticus being the one most frequently affected forty three occurred in the quadriceps femoris thirteen in the adductor muscles of the thigh two in the gluteal muscles one in the muscles of the ball of the thumb and one in the temporal muscle (Lewis)

A typical history is as follows a white male aged 17 complained of swelling of the thigh following a kick two weeks previously X ray showed calcification outside the femur A segment of fleshy white tissue was removed for biopsy X ray examination showed new bone formation in the periosteum and the soft tissues. Without a clinical history an inexperienced radiologist could easily diagnose this

lesion as osteosarcoma. The section of the lesion showed excessive new bone formation and a rather cellular stroma. An inexperienced pathologist also might easily incorrectly diagnose this lesion as osteosarcoma (Fig 873) Zone phenomena can be extremely helpful in the diagnosis During the evolution of the process



Fig 868 —Monostotic Paget s disease of the tibia. The x ray shows both bone destruction and bone formation. The nature of the process was obscure until biopsy (W U neg 51 3657)

Fig 869 —Photomicrograph of typical Paget s disease with thick trabeculae and numerous scalloped cement lines. (High power)

bone formation matures peripherally For example in a lesion approximately 6 weeks old the centrally placed areas may be quite cellular and impossible to differentiate from osteosarcoma. Poorly defined osteoid, arranged in an orderly pattern, occurs in the intermediate zone. *Excellent* bone maturation with ossifica

tion occurs at the peripheral margins (Figs 870-873) This condition must be differentiated from extraosseous osteosarcoma Undifferentiated tumor extends throughout the latter lesion without zone formation (Fine) We have not seen



Figs. 870 and 871 —Gross photograph of well-defined myositis ossificans occurring in muscle The roentgenogram shows bone formation in the periphery (W U negs 56-6193 and 55-6190) (From Ackerman, L. V J Bone & Joint Surg 40-A 279 1958)

myositis ossificans develop into osteosarcoma. We believe that previous cases reported represent parosteal osteosarcoma. The typical radiograph and the microscopic pattern of a sarcomatous stroma intermingled with adult bone is sufficient to make this differential diagnosis

Melorheostosis

Melorheostosis is a term derived from Greek words meaning flowing limb The proliferation of ivory like bone may be periosteal or endosteal. Bony tissue also is deposited in soft tissues in the region of joints In five biopsied cases the trabeculae were compact, the haversian canals normally outlined and the marrow fibrotic (Franklin) The excessive bone may cause locking of joints and bowing of long bones (Kirby) Associated soft tissue calcification is common.

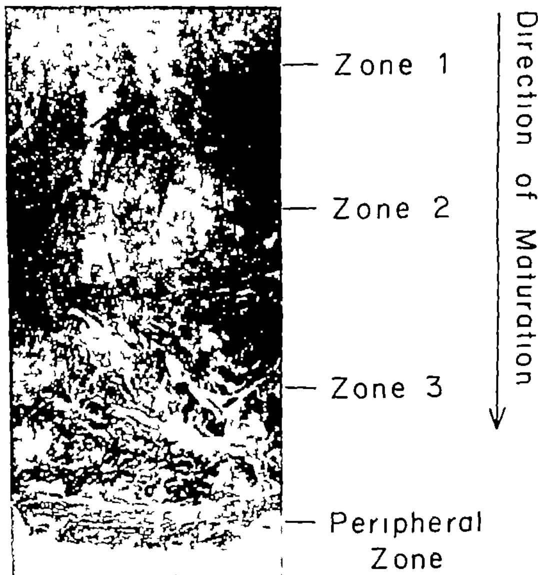


Fig. 872.—Schematic representation of zone phenomena in myositis ossificans (W U neg. 57 1517) (From Ackerman, L. V J Bone & Joint Surg 40-A: 279 1958)

GANGLION

Ganglia occur about joints and rarely about tendon sheaths They are annoying deformities which may cause some pain weakness and partial disability of the joint Individuals using the wrist and fingers a great deal (pianists typists)

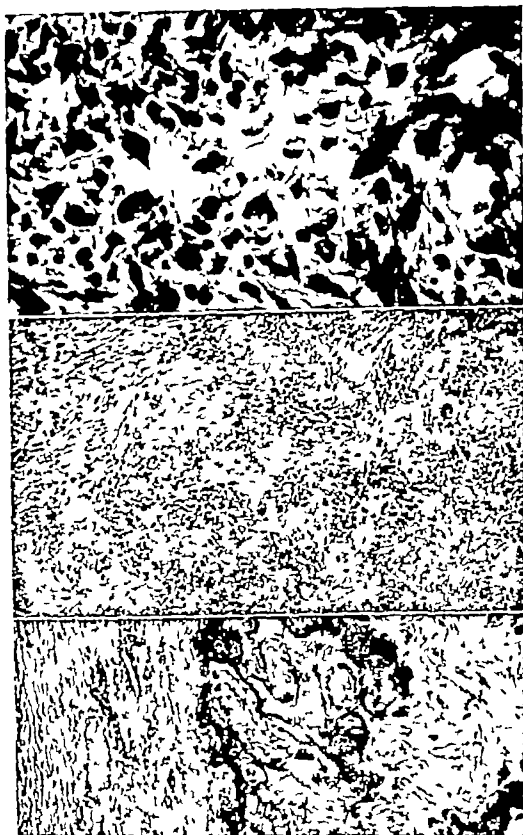


Fig 873 Three photomicrographs demonstrating zone phenomena. *A* is undifferentiated in pattern *B* demonstrates attempts at orientation of osteoid *C* the most peripheral, shows excellent bone formation (×450) (W U negs 55-6881 55-6880 and 55-6879) (From Ackerman L. V J Bone & Joint Surg 40-A 279 1958)

may develop ganglia. There may be a history of injury preceding ganglion formation. Ganglia develop by myxoid degeneration and cystic softening of the connective tissue of the joint capsule or tendon sheath (Lichtenstein) Doyle believes that a rent in the synovial membrane of a joint leads to the collection of synovial fluid and the formation of a false capsule. The most common location is on the dorsal carpal area of the hand where the cystic lesion pushes its way toward the surface between the tendons of the extensor indices proprius and the extensor carpi radialis (Fig 874) The second most common location is the volar surface of the wrist, superficial and medial to the radial artery They can also arise on the volar surfaces of the fingers just distal to the metacarpophalangeal joints Ganglia are not lined by synovia but contain clear fluid (Fig 875)



Fig 874 —Clinical photograph of the typical location and appearance of a ganglion. (W U neg 49-1173)

Fig 875 —Gross photograph of a ganglion. Note mucoid appearance and poorly defined capsule. (W U neg 50-3032)

GIANT CELL TUMOR OF TENDON SHEATH

Benign Giant Cell Tumor of Tendon Sheath (Xanthogranuloma, Fibrous Xanthoma, Myeloplaxoma Benign Synovium)

The so-called giant cell tumor of tendon sheath is a common lesion which occurs more frequently in females than males usually appearing in young and middle aged persons. It is practically always distributed between wrist and finger tips and between ankle and toe tips It is a single lesion measuring between 1 and 3 cm. in most instances. It is more often proximal than distal and most frequently on the

flexor surfaces It appears to have a fairly well-defined capsule and varies in color from whitish gray to yellowish brown It may be somewhat lobulated

Microscopically this lesion arises from the inner layer of the tendon sheath is pigmented, and contains closely packed polyhedral cells which develop phagocytic properties Giant cells containing fat and hemosiderin often are present. (Fig 876) Cells in zones of active proliferation may show mitotic figures Focal zones of hyalinization are in the more quiescent areas The great cellularity of this tumor its variable pattern and the presence of mitotic figures may lead to an erroneous diagnosis of sarcoma However, these tumors are not malignant. They may erode contiguous bone by pressure If incompletely removed they may recur locally New lesions also possibly develop after excision (Jaffe, Wright)



Fig 876—Photomicrograph of a rather cellular giant cell tumor of tendon sheath origin. Giant cells are prominent and mitotic figures are rare (×200) (W U neg 50-1422.)

PIGMENTED VILLONODULAR SYNOVITIS AND BURSITIS

Pigmented villonodular synovitis and bursitis are histogenetically similar to benign giant cell tumors of tendon sheath (Jaffe) The synovitis tends to occur in young persons. In most instances synovitis appears in the knee joint. Although the knee joint is the commonest site the process may rarely involve such joints as the ankle hip shoulder or even the elbow Usually only one joint is involved, but rarely multiple joints have been affected Twenty of 28 cases reported by Atmore involved the knee joint. It may be focal or diffuse. When diffuse, it is made up of brownish yellow spongy tissue. Its appearance depends upon the content of hemosiderin pigment. Large amounts of tissue may be present and complete removal is impossible (Fig 877) The giant cell tumor of the tendon sheath grows toward the skin while this lesion grows into the joint space. Microscopically the cellular component is similar to that of giant cell tumor of tendon

sheath but in addition there are papillary projections made up of foam cells and hemosiderin containing phagocytes (Fig 878) The same type of lesion occurs more rarely in the bursa.

This lesion can be treated by excision it may locally recur because complete removal is impossible. If it locally recurs irradiation therapy may be helpful. In our experience this lesion has not become malignant. Extensively recurrent lesions however have been misdiagnosed as fibrosarcoma and synovial sarcoma.

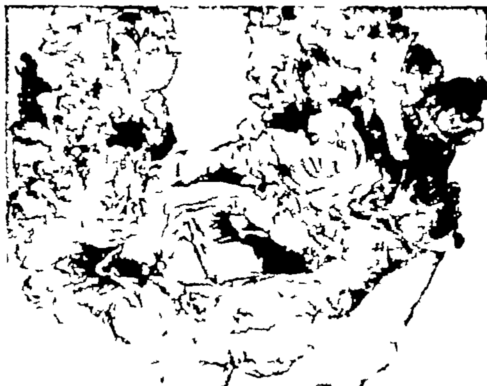




Fig 877 Gross photograph of a large mass of papillary brown tissue removed from th knee joint of a patient with villonodular synovitis (W U neg 50-3300)

Fig 878 Photomicrograph of papillary projections in pigmented villonodular synovitis. (×120) (W U neg 50-3948)

Bursae are found where muscles tendons and skin glide over bony prominences. They are subject to all the diseases that occur in large joint spaces Inflammation may be associated with the formation of cysts, fluid, and loose bodies (Fig 879) The incomplete removal of loose bodies may be followed by the disappearance of the remaining ones from the bursa A Baker's cyst occurs in the popliteal space from herniation of the synovial membrane through the posterior part of the capsule, or from escape of joint fluid through normal anatomic con



Fig 879 —Gross photograph of a bursal cyst of the prepatellar area. This cyst contained fluid. There is extensive proliferation of the synovia. (W U neg 51-40)

Fig. 880 —Gross photograph of a large Baker cyst The synovial membrane is chronically inflamed and loose bodies are present. (W U neg 47-4094)

nections of the knee joint with a bursa (Meyerding) (Fig 880) Another common lesion is subdeltoid bursitis associated with calcareous tendonitis. This entity is primarily a degeneration of a tendon or muscle in the rotator cuff of the shoulder followed by deposition of calcium in necrotic collagenous tissue. This calcific *material stimulates a secondary inflammatory reaction (Pederson)*

SYNOVIAL OSTEOCHONDROMATOSIS

Synovial osteochondromatosis is an infrequent disease of unknown etiology associated with the formation of osteocartilaginous bodies in the synovial membrane. This condition most commonly is monoarticular affecting the knee or hip and communicating bursae. It is aggravated by infection and trauma. Grossly the osteocartilaginous bodies may remain confined to the synovium or be extruded within the joint cavity They usually are partially calcified (Fig 881) Innumerable small bodies can be seen grossly in the resected lesion (Figs. 882 and 883) A single nodule beneath thinned synovium contains hyaline cartilage and at times bone (Fig 884) This lesion does not become malignant (Leydig)

ARTHRITIS

Degenerative Joint Disease (Osteoarthritis)

Surgical pathology specimens of legs amputated for traumatic reasons or because of gangrene secondary to vascular disease offer the unique opportunity for study of degenerative joint disease. The term osteoarthritis is not used because this type of joint disease is degenerative and not systemic. The bone and joints affected are conditioned by use and occupation of the patient (Keefer) changes in the knee joint are related directly to age. Both Bennett and Collins (1949) have described and illustrated these changes beautifully The classical monograph by Nichols and Richardson in 1909 summarized the pathologic alteration so well that we have little to add today Bauer summarized their classic article as follows

> In degenerative arthritis, the earliest and primary change in the joints is a gradual and uneven degeneration of the hyaline cartilage of the articular surfaces This is first detected as a fibrillation of the cartilaginous matrix which generally begins near the articular surface and is associated with a disappearance of the spindle-celled perichondrium. As a result of this fibrillation which takes place usually at right angles to the articular surface, the neighboring cartilage cells are set free and finally disintegrate and disappear Also the original smooth articular surface takes on a papillary appearance. At times this fibrillation is responsible for the freeing of minute masses of cartilage and fibrillated matrix. The depth to which this fibrillation extends varies. Sometimes it extends entirely through the cartilage down to the zone of provisional calcification so that masses of cartilage may be peeled away, exposing either the zone of provisional calcification or the underlying bone to the attrition of joint motion [Fig 885] Occasionally only a portion of the articular cartilage undergoes degeneration fibrillation and destruction [Fig 886] This leads to thinning of the cartilage over a circumscribed area. To meet this erosion and depression, an overgrowth occurs on the opposite joint surface This is brought about by increased activity of the peri

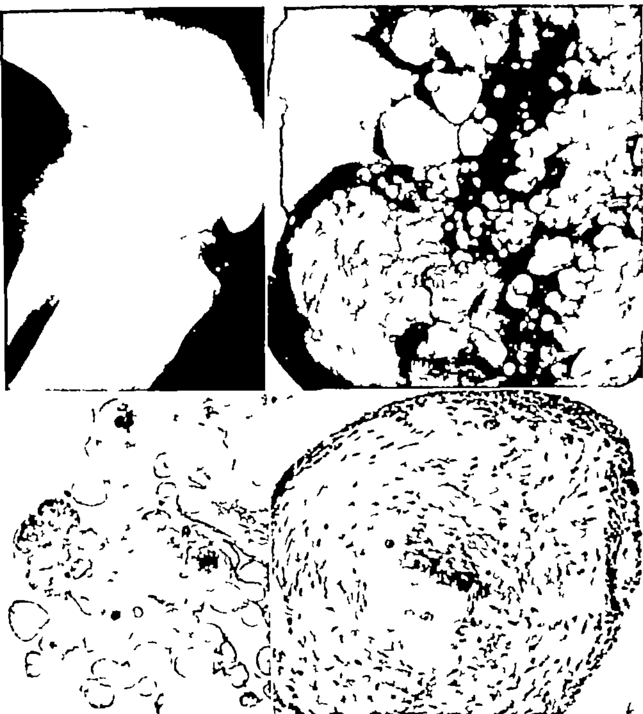


Fig 881.—Roentgenogram of synovial osteochondromatosis. The nodules can be seen clearly in the joint space. (W U neg 49-4113)

Fig 882.—Gross photograph of extensive involvement of the synovium of the knee joint by chondromatosis. (W U neg 48-3983)

Fig 883.—Photomicrograph demonstrating the pattern and formation of synovial chondromatosis. (Low power) (W U neg 48 3981)

Fig 884.—Photomicrograph of a single nodule of chondromatosis forming beneath the intact synovium. Note cartilage formation in the center of this nodule. (High power) (W U neg 48-3972.)



Fig 885 —Gross photograph of pronounced degenerative joint disease in a 55-year-old man Note degeneration and destruction of cartilage over a wide area (W U neg 52 3896.)

Fig 886 —Photomicrograph of a section taken through the zone shown in Fig 885 demonstrating fragmentation and fibrillation of thinned cartilage. (Low power) (W U neg 52-4490)

chondrium. As a result an irregular or somewhat toothed joint line is formed and finally with ultimate disappearance of the entire articular cartilage the two bony surfaces are brought into contact Since this change takes place gradually and is at first confined only to a portion of the joint, motion is continued with the result that the exposed bone undergoes marked thickening of the trabeculae and narrowing of the marrow spaces until an extremely dense bony structure has been produced The friction of continued joint motion produces a high degree of polish on the exposed condensed bone which then acquires an appearance closely resembling ivory hence the term eburnation of bone

While this process of fibrillation and destruction of cartilage with erosion is taking place in one portion of the joint and a corresponding overgrowth is occurring on the opposite joint surface secondary changes in the joint may be produced Changes in the shape of the joint surface may gradually over a period of months or years lead to more or less extensive subluxations As a result the amount of joint motion may be diminished or in certain instances the joint surfaces may become interlocked, producing ankylosis by deformity There is no true ankylosis in this type of joint disease. Common among these imperfectly understood secondary changes is an increased activity of the perichondrium at the periphery of the joint where the cartilage and capsule come together This results in the new formation of cartilage which may be transformed into bone and thus causes an increase in the size of the bone end. As a rule this increase in circumference is not uniform, but is irregular and the contour is nodular as exemplified by Heberden s node Since this deposit of new bone is usually within the attachment of the joint capsule it may in some cases lead to filling up of the original joint cavity thus producing partial or complete dislocation.

As a rule, no great increase in the thickness of the joint capsules of these joints is observed and in many instances, the synovial membrane appears normal However in some cases there is marked thickening of the synovial membrane with the production of papillary or pedunculated masses of connective tissue which may be converted by metaplasia into cartilage or bone or, in some cases into fat tissue. Detachment of these pedunculated masses may give rise to loose bodies the so-called joint mice. The breaking off of an osteophyte is another cause of loose body formation As a rule in this type of joint disease there is very little tendency for the synovial membrane to extend over the articular surfaces and in no case does fibrous ankylosis occur

Nichols and Richardson also called attention to the fact that there is no evidence of inflammatory exudation in early degenerative joint disease.

The cartilage is the key to the changes in osteoarthritis. Its capacity for repair is feeble. In certain areas of the hip joint not exposed to pressure or friction (Harrison) cartilage changes take place although they are most common on the joint surface exposed to friction weight bearing or movement (Collins, 1955) There is loss of chondroitin sulfate matrix in the cartilage in advance of actual mechanical attrition (Matthews) With degeneration of cartilage the stability of the chondro-osseous junction is lost and narrowing of the joint space is in fact loss of cartilage thickness. If the osteoarthritic head of a femur is examined cysts frequently are found close to the surface where they may communicate with the joint and are surrounded by dense bone. The cyst may be replaced by fibrous tissue or contain fluid (Figs 887 and 888) (Harrison)

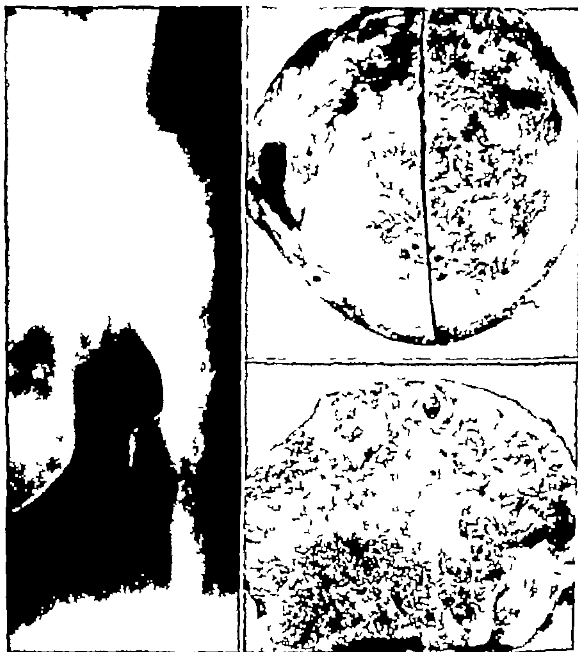


Fig 887 —Roentgenogram of head of femur and gross photographs of this head to demonstrate advanced osteoarthritic changes. There is loss of cartilage and cyst formation. (W U negs. 54-1439 54 1?/3 and 54-1274)



Fig 888—Two photomicrographs show in finer detail the loss of cartilage the eburnation and the cyst formation in Fig 887 (Low power) (W U negs. 54-1493 and 55-34)

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic polyarticular arthritis of unknown etiology It is most common in women during the second and third decades. The joints of the feet and hands are the most commonly involved. Others commonly affected are the elbows knees, wrists, ankles hips spine, and temporal mandibular



Fig 889 —Gross photograph of advanced rheumatoid arthritis involving the femur There is prominent proliferation of synovium and partial to complete destruction of the overlying articular cartilage. (W U neg 49 5578)

area. The earliest changes occur in the synovial membrane. Hyperemia of the synovium is followed by active cellular proliferation and infiltration by plasma cells and round cells (Allison) The synovial changes are not specific (Sherman) In the second phase, granulation tissue grows into the subchondral marrow of the bone Osteoporosis occurs early There is prominent pannus formation over the articular cartilage (Fig 889) Cartilage and even bone form in this pannus. The granulation tissue of the subchondral area and the pannus within the joint

attack the cartilage Its destruction may be followed by fibrous ankylosis and eventually bony ankylosis. Different pathologic stages of the process occur in different joints at the same time (Pirani) Tenosynovitis is present Nodules occur in the tendons and tendon sheaths which have centers of fibrinoid necrosis. Rheumatoid nodules sometimes develop in tendons causing inflammation and thickening (Kellgren) The relation of rheumatic heart disease to rheumatoid arthritis is unknown. Baggenstoss found cardiac lesions in 25 cases of rheumatoid arthritis which he identified as rheumatic in nature Joint changes present in rheumatic

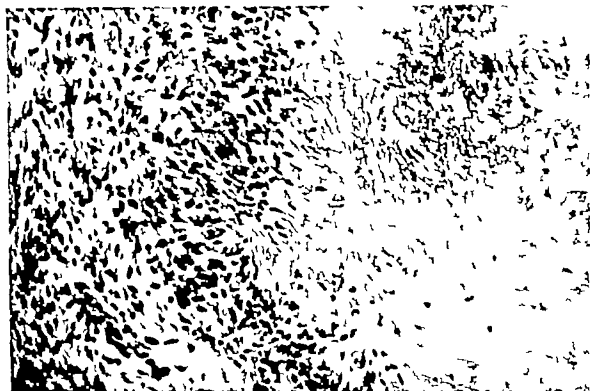


Fig 890 —Photomicrograph of a typical nodule in rheumatoid arthritis. There are central necrosis palisading of cells around the margin of this area, and chronic inflammatory cells. (×200) (W U neg 49-4145)

heart disease are indistinguishable from those of rheumatoid arthritis without heart involvement. In both conditions subcutaneous nodules are present, but Bennett has pointed out differences in their microscopic pattern Luck states that nodules in rheumatoid arthritis last many months and nodules in rheumatic fever last only days or weeks. The microscopic differences cited by Bennett are not diagnostic of a specific nodule he emphasized that fibrinoid" change is predominant in rheumatic fever while necrosis and degeneration occurred primarily in rheumatoid arthritis (Fig 890) In addition small nodules identical with the myocardial Aschoff nodule were present in rheumatic fever Such Aschoff like nodules were not seen in the lesions of rheumatoid arthritis. Freund found similar nodules in the region of nerve fibers in muscle. These nodules were located primarily in the perineurium and epineurium.

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Chapter 22

SOFT TISSUES

INFECTIONS

Infections of subcutaneous tissues occur secondary to cutaneous visceral, or osseous infections trauma, or as a complication of operations. Rarely such infection may be hematogenous

The severity of the inflammatory reaction and the type of tissue response observed pathologically depends upon the type, dose and virulence of the infecting organism the resistance of the host tissues the presence or absence of necrotic tissue hematoma and foreign body and the anatomy of the infected area Clinical types of infectious processes such as hemolytic streptococcal gangrene, necrotizing fascitis and Meleney s synergistic gangrene must be diagnosed by clinical appearance and bacteriologic study All advanced pyogenic and necrotizing infections produce an acute inflammatory tissue reaction indistinguishable microscopically However the diagnosis of granulomatous infections may be made in some instances by proper staining and careful search of tissue sections for characteristic organisms (actinomycosis, blastomycosis, coccidioidomycosis and sporotrichosis) Tuberculosis also may be suspected histologically but proof of the significance of the occasional acid fast bacillus seen in tissue sections rests with culture and guinea pig innoculation. Certain granulomatous and chronic pyogenic infections as well as encysted hematomas may present clinically as soft tissue tumors (Pickett Michelson)

TUMORS

Introduction

The tumors of the soft tissue make up a large heterogeneous collection The distribution of the different types tabulated by Stout may be inaccurate because of the high percentage of referred cases (Table 42) This group of tumors is almost uniformly badly treated. Such poor treatment is related to lack of understanding of the pathology The soft tissues as discussed here include only soft tissues of the external surfaces. An attempt has been made to classify these neoplasms and to discuss their pathologic diagnosis and treatment. Certain lesions (dermatofibroma, Kaposi s disease, and mycosis fungoides) are arbitrarily assigned to the chapter on Skin.

TABLE 42. 1,349 MALIGNANT MESENCHYMAL TUMORS—SURGICAL PATHOLOGY LABORATORY COLUMBIA UNIVERSITY FEB 1 1906 TO SEPT 1 1951*

Fibrosarcoma	403	Malignant hemangiopericytoma	32
Myxoma	99	Kaposi's sarcoma	43
Liposarcoma	262	Lymphangiosarcoma	7
Leiomyosarcoma	117	Osteogenic and chondrosarcoma	
Rhabdomyosarcoma	112	(extraskeletal)	13
Malignant granular cell myoblastoma	4	Synovial sarcoma	38
Malignant organized granular-cell		Malignant mesenchymoma	78
myoblastoma	12	Malignant mesothelioma	40
Malignant hemangioendothelioma	34	Reticulum cell sarcoma	27
(Omitted All skeletal tumors lymphosarcomas, and neurogenous tumors)		Plasmocytoma	28

*Courtesy Dr A. P Stout.

Biopsy

The relatively untrained surgeon confronted by a soft tissue mass boldly excises or enucleates it, invariably inadequately He is surprised to find it malignant. At times he is too radical but more often too conservative. Because of poor primary treatment, the second corrective operation may have to be so radical that deformity or sacrifice of an extremity results The proper initial procedure is careful incisional biopsy After accurate classification of the tumor it can be treated intelligently Biopsy is not dangerous and does not cause spread. Indeed incisional biopsy followed by adequate treatment is associated with a lower incidence of local recurrence than is primary excision of the malignant soft tissue tumor when the latter is performed without prior biopsy (see Table 43) At the definitive operation the area of the biopsy should be entirely excised in continuity with the tumor Occasionally aspiration or needle biopsy of a soft tissue neoplasm may be diagnostic. We have not hesitated to use frozen section if a definite diagnosis can be made the lesion may be treated immediately Of course diagnosis by aspiration biopsy and/or frozen section may not be definitive. Treatment in these instances must be delayed until permanent section diagnosis is available. The importance of this concept is evident in the following three cases. A young ballet dancer noted a soft tissue tumor of the popliteal space. It was fairly firm and appeared to be deeply attached. The surgeon without biopsy started to remove the tumor found that it apparently infiltrated the deeper tissues, and sacrificed the leg Microscopic examination demonstrated that this was a fibrous tissue tumor of the desmoid type which could have been cured by conservative treatment and the extremity saved Conversely a young male with a soft tissue tumor in the region of the upper arm had careful incisional biopsy which showed desmoid tumor The tumor was excised locally without sacrificing the arm. The patient is still living 10 years later The third example occurred in a young male who had an apparently encapsulated soft tissue tumor on the upper inner thigh enucleated without biopsy The lesion was liposarcoma. It quickly recurred locally and required hemipelvectomy to encompass the recurrence. A primary diagnosis by incisional biopsy and a radical local excision might well have saved the lower extremity

Lieberman reviewed a series of patients with soft tissue sarcoma and demonstrated a high incidence of local recrudescence in those who had had excision without preliminary biopsy (Table 43)

TABLE 43 CLINICAL EVALUATION OF PRELIMINARY BIOPSY*

	NUMBER OF CASES	LOCAL RECURRENCES
Without biopsy	27	21 (78.8%)
With biopsy	12	2 (16 6%)
Totals	39	23 (59 9%)

*From Lieberman Z and Ackerman, L. V Surgery 35 350 1954

Many malignant soft tissue sarcomas appear grossly to be encapsulated this encapsulation is false (Fig 891) Therefore, attempts to enucleate fail. This pseudoencapsulation occurs commonly in fibrosarcoma liposarcoma, and synovial sarcoma. The pathologist who studies these lesions should make every attempt to

classify them accurately for this classification may in time prove increasingly useful from the standpoint of treatment and prognosis He must know the orientation of the specimen and the tissue sections so that he can state with certainty whether or not the lesion was adequately excised Enough sections must be made to ensure good representation Special stains may be helpful in classification increased fat within viable tumor cells may prove the tumor a liposarcoma. The



Fig 891 —Photomicrograph of a liposarcoma. In the center is a broad band of connective tissue capsule. Tumor is present on both sides of the capsule The surgeon felt that he had adequately excised this neoplasm however his plane of dissection was close to the capsule but through the tumor Therefore it recurred locally (×90) (W U neg 57 198)

pattern of the reticulin framework (Wilder stain) may demonstrate that the tumor is a fibrosarcoma or may lend support for a diagnosis of leiomyosarcoma. Demonstration of myofibrils and fibroglia fibrils may be helpful in classification It is imperative that proper sectioning good fixation and good control or special stains be available.

Tumors and Tumorlike Conditions Arising From Fibrous Tissue

Juvenile Fibromatosis, Fascial Fibromatosis Juvenile Aponeurotic Fibroma.— Stout has used the term juvenile fibromatosis to include a variety of different fibrous tissue proliferations which may be difficult to distinguish from true neoplasms (Fig 892) In the child we have often seen fibrous tissue proliferations

which were poorly circumscribed Stout has seen 74 such lesions in children up to the age of 15, and lists the following anatomic sites

Hands and feet	20	Ear	1
Neck	15	Eyelid	1
Shoulder and adjacent areas	14	Suprapubic and perineal	1
Buttocks—thigh and leg	12	Lung	1
Scalp	3	Mesentery	1
Abdominal muscles	2	Generalized	3

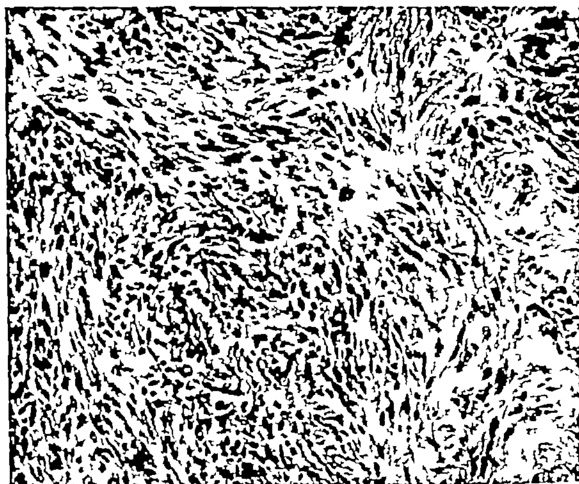


Fig 892 —Complicated fibrous tissue proliferation occurring in the submaxillary area following trauma. This is not sarcoma. (×260) (W U neg 56-748)

Konwaler has described another fibrous tissue proliferative lesion under the cumbersome term of subcutaneous pseudosarcomatous fibromatosis (fasciitis) (Fig 893) Keasbey has described an unusual lesion with a distinctive microscopic pattern under the term juvenile aponeurotic fibroma. This lesion occurs in children forms a soft tissue mass and frequently recurs microscopically it is highly cellular infiltrates voluntary muscle and contains deposits of calcium granules in peculiar linear palisades.

We have seen all of these lesions. They are frequently referred to us with the possible diagnosis of fibrosarcoma. Usually they are in children, and often the diagnosis is extremely difficult. We have been suspicious that the lesion is benign

particularly when it occurs in a child has poorly defined margins and shows little mitotic activity We have tended to treat these lesions conservatively even when they recur Rarely amputation may be necessary in stubbornly recurrent fibromatosis

Palmar and Plantar Fibromatosis.—Fibromatosis of the palmar and plantar fascias is a lesion of unknown etiology in which there is overgrowth of fibrous tissue. The plantar fascial lesions are much more common. In 69 cases of plantar fibromatosis 45 also had involvement of the palmar fascia. They grow slowly and form a considerable mass. On section the process is not encapsulated usually excisions are not adequate Nodules of fibromatosis may become 3 or 4 cm in the

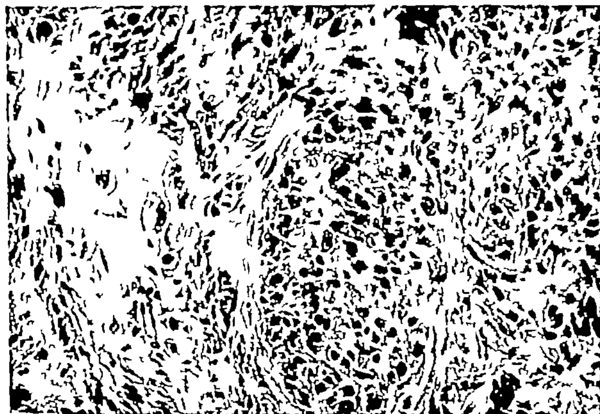


Fig 893—Photomicrograph of fasciitis recurrent in a child. This highly cellular lesion is often mistaken for sarcoma. (×275) (W U neg 58-4084)

plantar fascia. Microscopic examination often shows rather cellular well-differentiated fibrous tissue cells. Normal mitotic figures may be present This process may affect both the plantar fascias simultaneously or only one may be involved initially and the other several years later Palmar fascia may be involved but usually not to such an extent. This lesion may be so highly cellular that it is incorrectly diagnosed microscopically as a malignant neoplasm (Skoog Pickren) (Fig 894) Some of these lesions recur after inadequate excision Fibrosarcoma of the plantar and palmar areas is practically unknown (Allen)

Congenital Torticollis.—Congenital torticollis is a disease of unknown etiology characterized by fibrosis of the sternocleidomastoid muscle appearing shortly after birth. The child has "wryneck." The only cure is resection of the muscle Gross

examination shows fibrous replacement of the muscle. Microscopic examination shows fibrous tissue extending between and replacing muscle bundles (Fig 895) The cellularity of this fibrous tissue depends upon the age of the process. This condition has been considered due to a birth injury but we have never seen evidence of previous hemorrhage and do not have a good explanation for it (Brown)

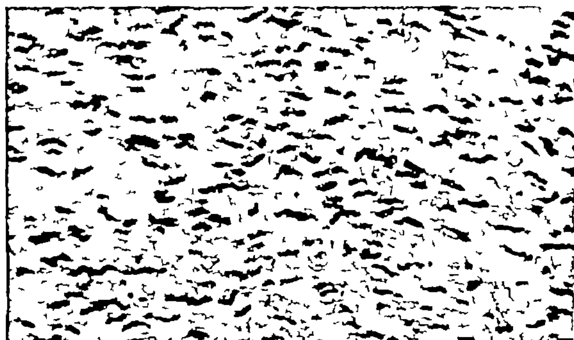


Fig 894 —Photomicrograph of a highly cellular area in plantar fibromatosis, often incorrectly diagnosed as fibrosarcoma. Note uniformity of nuclei. Mitotic figures usually are rare. (×400) (W U neg 52 3448)

Desmoid Tumors.—Desmoid tumors occur for the most part in the abdominal wall of females. They are thought by many to be the result of hemorrhage following prolonged labor but there is no evidence to support this. These lesions probably are not true neoplasms They represent an ascending level of aggressiveness compared to plantar and palmar fibromatosis. These lesions involve muscle, grow to a large size, and are not encapsulated (Fig 896) They are firm and may become fixed to the surrounding structures such as bone. Because of fixation and nonencapsulation they often are incorrectly diagnosed as malignant neoplasms clinically Microscopically well-differentiated masses of fibrous tissue infiltrate between muscle bundles (Fig 897) The fibrous tissue is well differentiated only normal mitotic figures are seen. Simple excision of the tumor is adequate. We have not seen this lesion metastasize, although local recurrence may occur (Masson) Extra abdominal desmoid tumors are less common than those of the abdominal wall they arise from musculoaponeurotic structures and have the same gross and microscopic pattern (Musgrove) In Musgrove s cases, 14 of the 34 followed some form of trauma. We have seen such a lesion in the abdominal wall following operation. Grossly they have a hard rubbery consistency cut with a creaking sensation and have glistening whitish pink color The larger lesions may contain zones of myxomatous and cystic degeneration. Microscopically evi

dence of previous trauma such as hemosiderin pigmentation is absent The lesion should be widely excised. The excision however should not sacrifice major blood vessels nerves or an extremity, even though recurrence may occur Recurrences may still be treated by local excision with chance of control We have found the incidence of local recurrence to be high after excision of extra abdominal desmoids Indeed some have recurred as many as five or six times Only rarely, however has local aggressiveness of the tumor forced amputation



Fig 895 —Photomicrograph of sternocleidomastoid muscle in congenital torticollis (wryneck) *Note fibrous tissue growing between muscle bundles.* (×680) (W U neg 49-5370)

Desmoids in children show a high frequency of local recurrence. Booher reported a desmoid of the abdominal wall which recurred and finally caused the death of the patient by extensive local spread. There were no distant metastases.

Dermatofibrosarcoma Protuberans.—Dermatofibrosarcoma protuberans is a cumbersome name used for a neoplasm of connective tissue origin. This neoplasm arises just beneath the overlying epidermis and forms single or multiple nodules (Darier Hoffman) It grows slowly and eventually forms a bulky mass (Fig 898) Well-defined nodules which are usually sharply delineated are seen on cut surface (Fig 899) Microscopically it is made up of very well-differentiated fibrous tissue cells, which usually contain only a few normal mitotic figures (Fig 900) It is impossible to make the exact diagnosis microscopically Postexcisional prognosis is excellent. Rarely they may recur only one case with distant metastases has been reported (Penner)

Fibrosarcoma.—Fibrosarcomas are the most common malignant tumors of soft tissue if the retroperitoneal space and the mediastinum are excluded They occur in patients of any age. They arise from such superficial and deep connective tissues as fascia, tendon periosteum, and scar They grow slowly or rapidly and



Fig. 896 —Gross photograph of a large desmoid of the abdominal wall. Note lack of circumscription and almost complete replacement of the muscle (W U neg 50-5320)

Fig 897 —Photomicrograph of a desmoid tumor with adult fibrous tissue growing between muscle bundles. (Low power)

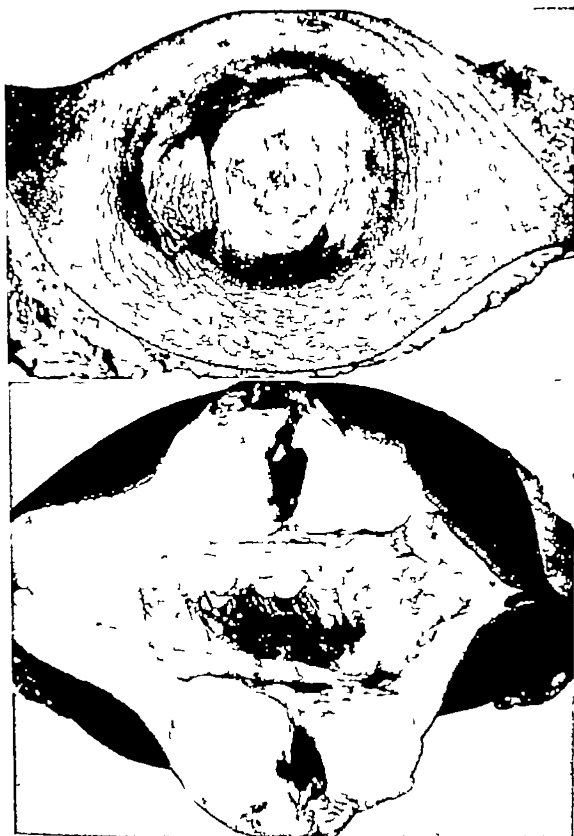


Fig. 898.—Gross photograph of dermatofibrosarcoma protuberans occurring in the buttock demonstrating multinodulation (W U negs. 57 5211 and 57 5212.)

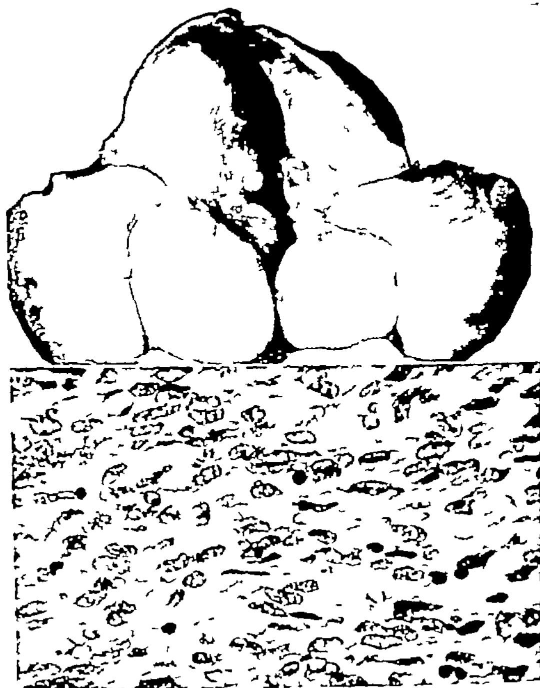


Fig 899 —Gross photograph of a dermatofibrosarcoma protuberans showing the multiple nodules without necrosis

Fig. 900 —Photomicrograph of a dermatofibrosarcoma protuberans with well-differentiated fibrous tissue cells without mitotic activity (×600) (W U neg 52 136)

often appear well-encapsulated (Fig 901) They are usually soft, cellular and contain areas of necrosis and hemorrhage Microscopically the well-differentiated tumors are easily recognized as fibroblastic (Fig 902) The individual cells resemble fibroblasts and a Wilder stain demonstrates abundant reticulin wrapped around each cell (Stout) Phosphotungstic acid hematoxylin stains abundant intercellular fibroglia fibrils The fibroblastic nature is more difficult to recognize in the undifferentiated tumors. When other neoplasms particularly the liposar



Fig 901 —Gross photograph of moderately differentiated fibrosarcoma of the thigh. Apparent encapsulation is in contrast to lack of circumscription in the desmoid. (W U neg 46-2006.)

Fig 902 —Photomicrograph of well-differentiated fibrosarcoma showing fibroblasts with occasional mitotic figures. (×600) (W U neg 52 3454)

coma, are undifferentiated they may closely resemble fibrosarcoma. The presence of tumor giant cells in a malignant soft tissue sarcoma usually means that it is not fibrosarcoma but more probably rhabdomyosarcoma or liposarcoma. The treatment of choice is radical excision Generally the more superficial and differentiated the tumor the better the patient s prognosis.

Tumors of Nerve Sheath Origin

Neurilemoma.—There are two distinct neoplasms of nerve sheath origin the neurofibroma and the neurilemoma. Both may be present in von Recklinghausen's disease, but the neurilemoma usually is seen without other manifestations. Both types may occur together It is important to distinguish between these two types because the neurofibroma may become malignant while the neurilemoma is invariably benign. These tumors occur in the mediastinum and retroperitoneal areas (see Chapters on Mediastinum Peritoneum and Retroperitoneum)



Fig 903.—Gross photograph of an encapsulated neurilemoma with a small nerve entering its periphery (W U neg 52 1170)

The neurilemoma is an *encapsulated* neoplasm occurring most commonly on flexor surfaces. It does not often grow to a large size it rarely is multiple. It may be cystic when it reaches 3 to 4 cm. in diameter Invariably it is attached to nerve (Fig 903) It may be recognized clinically because of its location cystic nature, and association with a nerve. Microscopically two types of tissue are seen Antoni type A and Antoni type B (Fig 904) The Antoni type A consists of masses of cells with palisading of the nuclei (Fig 905) The type B tissue is myxomatoid and usually contains cystic spaces. Thick walled blood vessels are often observed. Special stains for neurites demonstrate them only in the capsule Removal is curative. If radical removal compromises function because of nerve injury (for example facial nerve) conservatism is justified since the tumor only has the capacity to recur locally (Roos)

Neurofibroma.—The various manifestations of neurofibromas are legion. Florid von Recklinghausen's disease consists of innumerable neurofibromas of varying sizes and shapes, usually associated with café-au lait spots These innumerable peripheral tumors are infrequently associated with deep-lying soft tissue osseous, retroperitoneal posterior mediastinal, or orbital lesions The peripheral neurofibromas usually do not become malignant, and the only reasons for surgical re-

moval are size and unsightliness (Fig 906) When the neurofibromas become large and grow in the deeper areas such as the axilla thigh or buttock, they should be resected because they may undergo malignant change (McCarroll) These lesions



Fig 904—Photomicrograph to demonstrate the Antoni type A (cellular areas) and Antoni type B (cystic areas) (Low power) (W U neg 50-438)

Fig 905—Photomicrograph of an area of type A tissue with palisading of cells. (×210) (W U neg 50-439)

may form diffuse nodular enlargement of peripheral nerves designated as a *plexiform neurofibroma* (Fig 907) They may involve the nerve diffusely making resection in one area only palliative because other lesions may later become manifest. Microscopically these lesions are *nonencapsulated* they form disorderly



Fig 906 —Clinical photograph of a patient with von Recklinghausen's disease with innumerable nodules and café-au-lait spots. (W U neg. 49-6545) (Courtesy Dr H R. McCarroll, St. Louis Mo)



Fig. 907 —Gross photograph of a plexiform neurofibroma which occurred in the nerves of the lower extremity of a young boy Note gigantic nerve bundles. (W U neg. 52-4785)

masses of tissue which are not often recognized as being neurofibromatous Connective tissue proliferation is extremely abundant. The changes seen are related to the fibrous proliferation within and around the schwannian sheath (Fig 908)

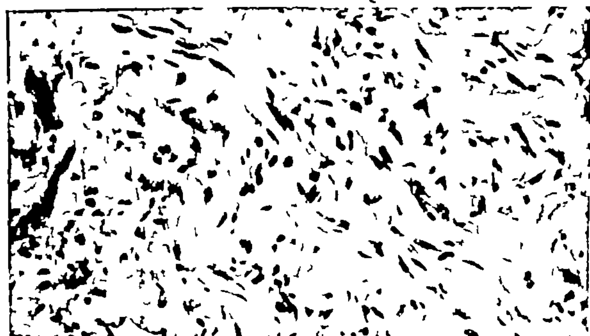


Fig 908.—Photomicrograph of a typical neurofibroma. Note the disorderly pattern of the fibers. (×400) (W U neg 52 3602.)

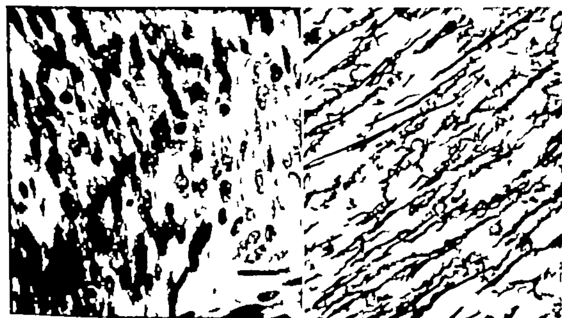


Fig 909—Photomicrograph of a fairly well-differentiated malignant schwannoma of the chest wall. (×400) (W U neg 50-5445)

Fig 910—The reticulin stain demonstrates that the thick wiry fibers run in long parallel lines between the tumor cells (×400) (W U neg 50-5446)

Malignant Schwannoma (Neurofibrosarcoma) —Malignant schwannoma is the preferred name for the malignant counterpart of the neurofibroma. This tumor is uncommon but during the 1930's neurofibrosarcoma was epidemic because of



Fig 906.—Clinical photograph of a patient with von Recklinghausen's disease with innumerable nodules and café-au lait spots (W U neg 49-6545) (Courtesy Dr H R. McCarroll St. Louis Mo)



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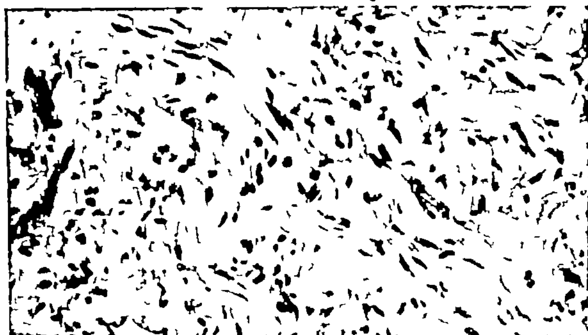


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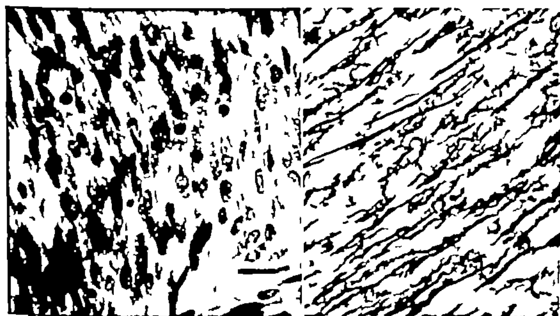


Fig 909 —Photomicrograph of a fairly well-differentiated malignant schwannoma of the chest wall. (×400) (W U neg 50-5445)

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Malignant Schwannoma (Neurofibrosarcoma) —Malignant schwannoma is the preferred name for the malignant counterpart of the neurofibroma This tumor is uncommon but during the 1930 s neurofibrosarcoma was epidemic because of

the popularity of this diagnosis. A microscopic diagnosis of early malignant change in a neurofibroma is quite difficult. The microscopic alterations are extremely subtle and consist only of slightly increased cellularity and beginning nuclear prominence (Fig 909) In fact, the diagnosis of benign neurofibroma may be made only to be followed by subsequent recurrence Review of all sections then shows that the tumor was malignant initially Reticulin stain demonstrates wiry fibers running in long lines between tumor cells (Fig 910) Malignant schwannomas tend to recur repeatedly before distant metastases appear Each recurrence may have increasing microscopic evidence of malignant change.

Tumors Arising From Fat

Lipoma.—Benign fatty tumors can arise in any location where fat is normally present (Stout) Although these tumors may be in the deep tissues, they are usually subcutaneous. In Pack's series there were about 120 lipomas to 1 liposarcoma. They may be single or multiple They grow to large size, are not well circumscribed, and consist of bright yellow fat separated by fine fibrous trabeculae. Areas of infarction necrosis, and calcification may occur Only rarely does lipoma become liposarcoma (Wright)

Liposarcoma.—Liposarcomas are relatively frequent neoplasms. They often grow large and occur most commonly in the soft tissues of the thigh and buttocks. They are the most common primary retroperitoneal sarcoma (Fig 911) Grossly they often appear well circumscribed but this impression is false (Stout) They often have a mucoid slimy cut surface and are frequently mistaken grossly for myxoma (Fig 912) Others may mimic brain tissue their surface resembling cerebral convolutions. Microscopically the individual cells of well-differentiated tumors have uniform nuclei which are often crescent shaped because of compression by cytoplasmic fat (Fig 913) Undifferentiated tumors have considerable variation in microscopic pattern and contain bizarre tumor giant cells with vacuolated cytoplasm (Fig 914) These tumors frequently are enucleated only to recur locally spread, and eventually cause death This common soft tissue sarcoma may show striking radiosensitivity Occasionally these tumors have multiple foci of origin (Ackerman)

Hibernoma.—The hibernoma is a rare benign neoplasm occurring most commonly in the interscapular region and the axilla. It forms a soft tissue mass which is brown on section. The microscopic pattern is characteristic—an organoid arrangement of large cells which contain many vacuoles which stain with scarlet R (Fig 915) This tumor received its name because it is thought to arise from brown fat similar to that seen in the hibernating glands of animals (Brines)

Tumors of Lymphatic and Vascular Origin

Hemangioma.—The classification of hemangiomas is unsatisfactory About three fourths are present at birth about 60 per cent occur in the head and neck area. The spider type, often associated with liver disease has a central vein which, if occluded, destroys the tumor It does not show spontaneous regression The port wine type (nevus flammeus) occurs commonly in the skin of the face

and neck, the thorax, and at times on the extremities It is present at birth This lesion grows very slowly Its increase in size is proportionate to the growth of the patient In time it becomes nodular and soft Microscopically this erythematous lesion contains scattered, thin walled superficial telangiectatic vessels (Watson)



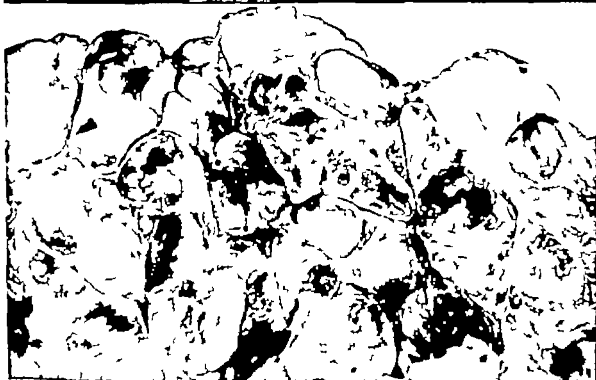


Fig 911 —Surgical specimen demonstrating the large size and typical location of a liposarcoma. (W U neg 49-607)

Fig 912 —Gross photograph of the tumor shown in Fig 911 demonstrating the typical appearance on cross section Note multiple nodules areas of hemorrhage and mucoid appearance of the surface. (W U neg 49-608)

It is radioresistant and does not regress spontaneously This lesion may become very large and unsightly its treatment is often difficult.

The so-called strawberry type of hemangioma is made up of cellular masses of closely packed endothelial cells with spaces containing relatively little blood

Fig 913 —Photomicrograph of extremely well-differentiated liposarcoma in which the individual nuclei have been compressed to a crescentic shape (×400) (W U neg 49 4502)

Fig 914 —Photomicrograph of a highly undifferentiated liposarcoma with innumerable tumor giant cells and great pleomorphism. Tumors with this microscopic appearance are often incorrectly diagnosed as rhabdomyosarcomas. (×360) (W U neg 51-804)



Fig 915 Photomicrograph of a hibernoma with large uniform cells. The vacuoles contain fat. (×480) (W U neg 49-6716.)

Only rarely does this type of hemangioma contain a significant cavernous component This hemangioma is present at birth or appears shortly after and grows rapidly during the first few months of life At this time it is highly cellular and contains many mitotic figures (Fig 916) The color is an intense crimson If

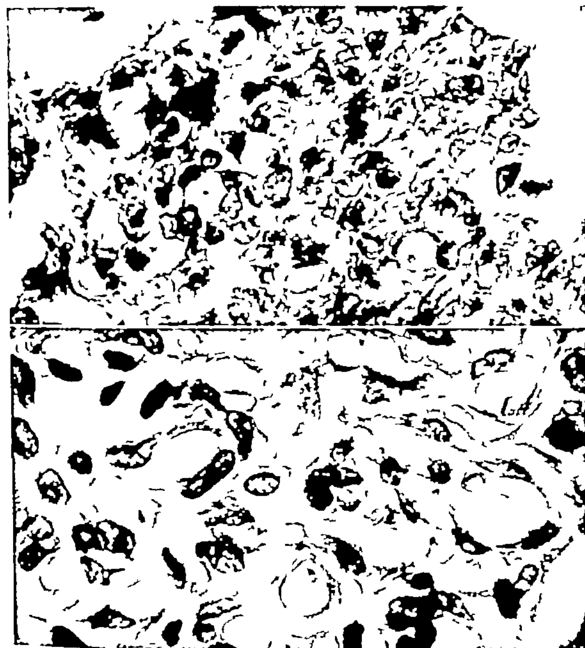


Fig 916—Photomicrograph of a highly cellular hemangioma (strawberry nevus) in a baby 1 month old. Note mitotic figures and solid masses of cells. (×480)

Fig. 917—Photomicrograph of hemangioma (strawberry nevus) in a baby 1 year old. Note vascular channels, decreased cellularity and increased connective tissue (×480.)

the child cries the surface of the nodule becomes smooth The lesion stops growing and begins to fade when the child is about 6 months old. It becomes flaccid, pale blue, and is covered with tiny wrinkles. If sections are taken at 9 months or later the intense cellularity and mitotic figures are absent and the connective tissue increased (Fig 917) Eventually it completely disappears (Fig 918) In

a group of 93 hemangiomas in 77 patients studied by Lister and followed from one to seven years 92 out of the 93 regressed There is no exception to the rule that hemangiomas growing rapidly during the early months of life subsequently regress and disappear after about five years (Modlin) A rapid initial



Fig 918—Two clinical photographs a baby 3 months old and the same child four years later The extensive hemangioma (strawberry nevus) completely disappeared without treatment. (Courtesy Dr John Modlin, Columbia Mo.)

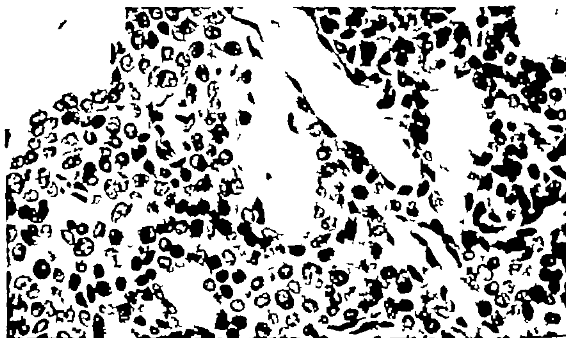


Fig 919—Photomicrograph of a typical glomus tumor with uniform cells and abundant vessels. It was exquisitely painful and located in the subungual area. The Cajal stain showed numerous neurites. (×500) (W U neg 52 3871)

growth rate is not present in the port wine type The strawberry type hemangioma must be sharply separated from the other varieties.

None of these hemangiomas become malignant. The so-called benign metastasizing hemangioma is a misnomer it represents angiosarcoma. The large deep

cavernous hemangioma may undergo thrombosis, ulceration or infection and become dangerous to life

Deep-lying cavernous hemangiomas may occur in the skeletal muscles (Fulton, Jenkins Jones) We have seen these lesions in the soft tissues of the thigh, back, and gluteal regions. They may form poorly circumscribed hemorrhagic masses with areas of organization and calcification Microscopically they contain cavernous spaces lined by normal endothelial cells Incomplete removal may cure or be followed by recurrence The lack of circumscription should not be construed as evidence of malignancy

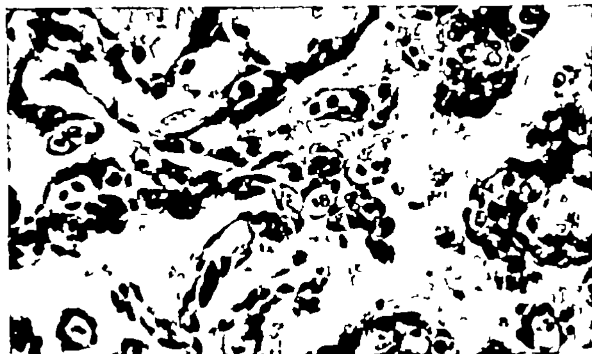


Fig. 920 —Photomicrograph of an angiosarcoma. Note layering of malignant cells and anastomosing channels. (×480)

Glomus Tumor.—The glomus tumor is an exquisitely painful neoplasm occurring most commonly in the subungual regions, flexor surfaces of the arms and the region of the knee They may appear in any location where a normal glomus is found. Such a lesion can even involve bone (Lattes) The glomus, a temperature regulating neurovascular structure, is an arteriovenous shunt abundantly supplied with nerve fibers. These lesions usually are small their vascularity varies Microscopically they consist of collections of uniform cells, smooth muscle and vessels a Cajal stain will show abundant nonmyelinated nerve fibers between the thick walled blood vessels (Fig 919)

Angiosarcoma (Malignant Hemangioendothelioma).—Angiosarcoma (malignant hemangioendothelioma) is a rare malignant neoplasm Stout collected only 14 from the soft tissues. It is highly vascular grows in muscle or deep tissues, and occurs at any age. The microscopic pattern is diagnostic and is accentuated by the silver reticulin stain. The tumor cells proliferate in the vascular lumina within the reticulin sheath They form layers and anastomosing channels (Fig 920)

Liposarcomas may contain vascular areas which resemble angiosarcoma. The other lesion which I have twice confused with it is metastatic carcinoma of the kidney The tumor cells in this lesion contain fat.

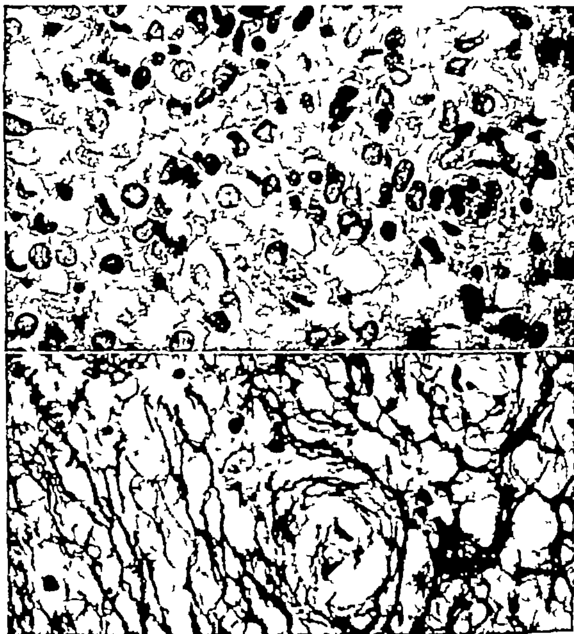


Fig 921 —Photomicrograph of a hemangiopericytoma with uniform cells and abundant vascularization. (High power)

Fig 922 —The reticulin pattern shows the tumor cells lying outside of the reticulin sheaths. (High power)

Hemangiopericytoma.—Hemangiopericytoma an infrequent soft tissue tumor invariably has a tan color (McCormack) Microscopically it has distinctive large masses of cells with oval vesicular nuclei, and is quite vascular (Fig 921) Recognition is certain only with the use of a reticulin stain. The tumor cells lie close to the wall of the vessels they apparently are related to Zimmerman's pericyte

a modified smooth muscle cell (Fig 922) The identification of this tumor type has been established not only by the appearance of the cells but also by tissue culture (Murray) Although their malignant nature is not clear microscopically the tumors locally infiltrate and metastasize Six of 35 hemangiopericytomas metastasized (Stout)

Hygroma (Diffuse Lymphangioma) —The lesion known as hygroma is a congenital malformation occurring in children it is a poorly defined soft tissue mass in the neck which consists of large lymphatic channels growing in loose connective tissue (Maxwell) (Fig 923) This lesion is usually posterior to the sternocleidomastoid muscle It may extend into the mediastinum This lesion does not become malignant it is cured by excision (Gross)



Fig. 923 —Clinical photograph of a large hygroma in a child. (From Maxwell, J H. South. M. J 45 292 1952.)

Lymphangiosarcoma.—Lymphangiosarcoma arises rarely in patients who have had long-standing massive lymphedema after radical mastectomy (Stewart) It may also develop secondary to chronic lymphedema of the lower leg (Hermann) These tumors are highly vascular and grow rapidly Microscopically they are composed of areas resembling angiosarcoma, and other zones with empty endothelium lined spaces suggesting lymphatics.

Tumors of Smooth Muscle Origin

Leiomyoma.—Vascular leiomyomas of the soft tissues are rare neoplasms. Multiple leiomyomas of the skin usually are superficial small and benign. They arise from the arrectores pilorum muscles (Lendrum) Single tumors can arise from smooth muscle bundles in the superficial subcutaneous tissue of the nipple axilla, anal region scrotum penis and labium majora (Stout) At times paroxysmal pain may accompany them.

Grossly they are yellow or yellowish pink and fairly firm. These benign-appearing neoplasms like those of the gastrointestinal tract, may metastasize. Microscopically these tumors in soft tissues are made up of large numbers of vessels, usually without elastic fibers which are mixed with smooth muscle bundles.

Leiomyosarcoma.—The leiomyosarcomas of soft tissue are even more rare in our experience than the vascular leiomyomas. Stout found only six in the extremities. Microscopically the individual cells have elongated blunted nuclei. Occasionally myofibrils are demonstrated (Fig 924) The phosphotungstic acid-hematoxylin stain of well-differentiated tumors infrequently shows terminal myofibrils with a hooklike appearance. The reticulin extends as wavy undulating fibers between long lines of tumor cells. Palisading of nuclei should not be a reason for calling one of these tumors neurogenous.

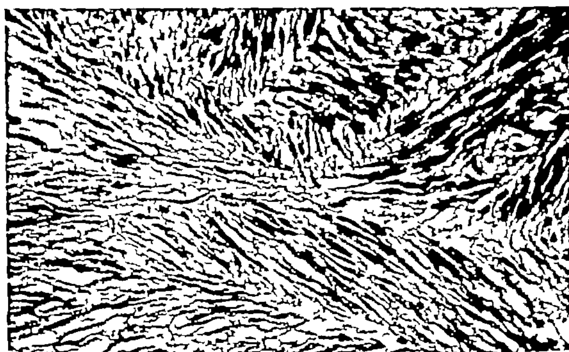


Fig. 924—Photomicrograph of a well-differentiated leiomyosarcoma. Note the pattern and the elongated and blunt-ended nuclei. (×400)

Tumors of Striated Muscle

Rhabdomyosarcoma.—Rhabdomyosarcomas make up only a small per cent of malignant soft tissue sarcomas. Stout collected 107 cases. These deep-seated tumors may be confined within fascial compartments and have the shape of the muscle from which they arise. Their growth rate often is rapid they may burst through the skin and form a fungating vascular mass (Fig 925) Rhabdomyosarcoma may take on different gross and microscopic patterns (Horn) In the botryoid form occurring in the bladder vagina and bile ducts it may grossly resemble a nasal polyp When it is superficial and just beneath a lining epithelium as in the bladder there is an undifferentiated cellular zone adjacent to the epithelium. The alveolar form, occurring in soft tissues and at times mistaken microscopically for reticulum cell sarcoma, has been well described by Riopelle (Fig 926) The



Fig. 925.—Gross photograph of a large fungating rhabdomyosarcoma of the soft tissue of the ankle

Fig. 926.—*A* Photomicrograph of alveolar form of rhabdomyosarcoma. This type is easily mistaken for reticulum cell sarcoma (×770.) (From Horn, R. C., Jr and Enterline H. T., Cancer 11: 181 1958.)

embryonal type most often found in the orbit in children has myxomatous zones and fibrosarcomatous areas (Stobbe) The microscopic recognition is simple in the well-differentiated ones containing cross striations (Fig 926) More often the tumors are highly undifferentiated Tumor giant cells are common in the pleomorphic classic type. They often have a tennis racquet shape with long tapering cytoplasmic bodies (Fig 927) Prognosis for the entire group is very poor (31 of 39 reported by Horn died)

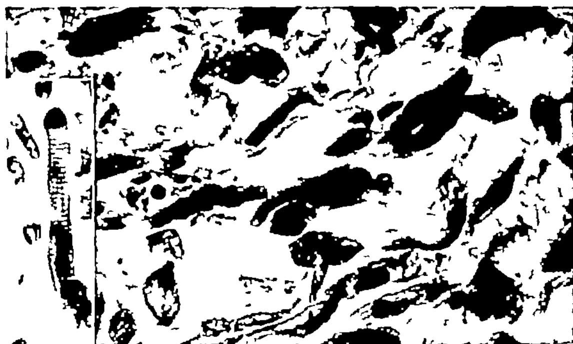


Fig 927 —Photomicrograph of a highly undifferentiated rhabdomyosarcoma with tumor giant cells and tapering cytoplasmic processes (High power) The cell in the inset shows well-defined cross striations. (High power) (W U neg 46-1718.)

Tumors of Synovium

Synovial Sarcoma.—The synovial sarcoma is a highly malignant tumor usually arising most commonly about the knee and ankle joints in young adults (about 80 per cent) (Fig 928) It also occurs about the shoulder and elbow we have seen two cases in the region of the hip This neoplasm grows very close to joints, tendon sheaths and bursae, but it is rare for it to involve the synovial membrane We have seen this tumor involve the synovium of the knee joint on one occasion. Grossly it forms circumscribed, firm grayish pink tumors. The circumscription is false Microscopically it has a sarcomatous stroma and pseudoglandular areas mimicking the arrangement of synovial membrane (Fig 929) The Schiff stain may show vacuoles within the glandular cells, suggesting the presence of hyaluronic acid. If the fibrosarcomatous area predominates the incorrect diagnosis may be fibrosarcoma the pseudoglandular zones may be mistaken for metastatic adenocarcinoma. These tumors metastasize to regional lymph nodes (10 to 15 per cent) The preferable treatment of such tumors is radical excision there should be no hesitation about amputation after the diagnosis has been estab-

lished by careful incisional biopsy. The results of treatment have been extremely poor; only rare cases are ever cured (Haagensen, Pack). The poor results probably are related to the long duration of the disease before diagnosis and attempts to save the extremity of young patients, which result in inadequate tumor excisions.



Fig. 928.—Clinical photograph of a recurrent synovial sarcoma of the ankle in a young man. It was inadequately excised, recurred and distantly metastasized, causing the death of the patient. (W U neg 48-192.)

Fig. 929.—Photomicrograph of a synovial sarcoma with a sarcomatous stroma and glandular zones. (×400.)

Tumors of Mesenchyme

Myxoma (Myxosarcoma)—This tumor arising from primitive mesenchyme occurs at all ages It has a mucoid slimy gross appearance. Microscopically it is made up of well-differentiated cells with even staining uniform nuclei (Fig 930) The cells are separated by mucoid material (hyaluronic acid) These tumors occur in the retroperitoneal area. As they grow in the soft tissues of the neck back thigh, or buttock, they locally infiltrate, stubbornly recur but do not distantly metastasize (Stout) Their failure to metastasize has been the reason for calling them myxomas. This entity is extremely rare in my experience several cases which I thought to be myxoma were proved to be liposarcoma.



Fig 930—Photomicrograph of a myxoma involving the soft tissue of the cheek. Individual cells are well differentiated and grow in a loose myxoid ground substance. (×1550) (W U neg. 48-3888)

Benign and Malignant Mesenchymoma.—The benign and malignant mesenchymoma should be mentioned. Mesenchymoma is a convenient name for it embraces the various tissues which can be present and indicates the versatility of the mesenchyme. The commonest benign variant is composed of smooth muscle, fat and blood vessels. We are not sure that this is a true neoplasm. The malignant variants, well described by Stout contain multiple varieties of malignant soft tissue sarcomas in the same neoplasm. In other words chondrosarcoma, liposarcoma and rhabdomyosarcoma may all be observed in a single tumor

Tumors Arising From Nonchromaffin Paraganglia

Tumors of this nature are usually designated as *carotid body tumors* However similar tumors arise from paraganglia in many other locations the glomus jugulare, ganglion nodosum of the vagus nerve (Coldwater) and aortic body

These interesting neoplasms do not produce epinephrine like substances as do the neoplasms arising from the adrenal medulla The nonchromaffin paraganglia are probably chemoreceptors (LeCompte) The neoplasms of the carotid body arise at the bifurcation of the carotid artery and become closely adherent to it (Fig 931) This firm adherence often has caused these tumors to be called malignant (Fig 932) They practically never metastasize We have seen only one with regional lymph node metastases (Sternberg) Grossly they usually do not reach large size. Often the clinical diagnosis is not made until its characteristic location is determined at exploration Frozen section should make the diagnosis. The surgeon must consider the operative risk (30 per cent) and high morbidity caused by damage to the central nervous system (80 per cent) before resecting the tumor It may be possible to remove the neoplasm without resecting the carotid artery (Lahey) The size of the tumor and the symptoms accompanying it may force arterial resection The use of arterial substitutes may reduce the danger of complete resection



Fig 931—Clinical photograph of a middle-aged woman with a large pulsating nonchromaffin paraganglioma (carotid body tumor) of the neck. This had been present for many years there were symptoms of obstruction. (Contributed by Dr James Barrett Brown St Louis Mo)

Microscopically these tumors are similar they have uniform nuclei no mitotic figures, an organoid pattern, and a characteristic arrangement of reticulin separating the cells into small nests (Figs 933 and 934) On rare occasions mitotic figures occur we observed a tumor of this type invading the nerve. Tumors of the *glomus jugulare* may invade the petrous portion of the temporal bone (Winship) We have seen a tumor arising from the ganglion nodosum of the vagus nerve surround and compress the esophagus It was incompletely removed several times.

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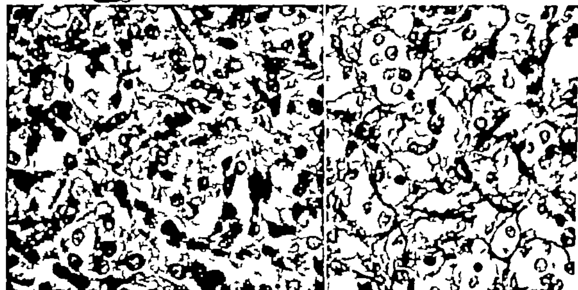


Fig 932.—The tumor shown in Fig 931 was resected, and it was found necessary to remove a segment of the carotid artery The gross photograph demonstrates an encapsulated neoplasm. It was vascular grayish pink in color and weighed 140 grams. (W U neg 51 5003)

Fig 933 —Photomicrograph of the tumor showing its cellularity organoid pattern, and lack of mitotic activity (×460) (W U neg. 51 5609)

Fig 934 —Photomicrograph of the tumor stained with a Wilder reticulin stain. Note that nests of tumor cells are encircled by characteristic black fibers. (×460) (W U neg 51 5609)

Tumors of Uncertain Histogenesis

Benign Granular Cell Myoblastoma.—Benign granular cell myoblastoma, probably a neoplasm occurs most commonly in the tongue It has been seen however in many other locations such as the skin vulva, breast larynx esophagus, bronchus appendix rectum anus urinary bladder, uterus and soft tissue We have seen six patients with multiple granular cell myoblastomas of the skin These tumors are usually small and have poorly defined margins The individual cells are large and their cytoplasm highly granular (Fig 740) If they grow near the surface of the epidermis changes occur which are often diagnosed incorrectly as carcinoma (Fig 935) The histogenesis of this tumor is uncertain (Pearse, Crane Fust) Tissue culture studies have not been definitive (Stout)



Fig 935.—Photomicrograph of the bizarre epidermal changes overlying benign granular cell myoblastoma. These changes often lead to an incorrect diagnosis of cancer (×125) (W U neg 52 3607)

Alveolar Soft Part Sarcoma (Malignant Nonchromaffin Paraganglioma Malignant Granular Cell Myoblastoma).—The histogenesis of alveolar soft part sarcoma (malignant nonchromaffin paraganglioma, malignant granular cell myoblastoma) also is uncertain (Christopherson) As far as is known transition between the benign granular cell myoblastoma and this neoplasm has not been observed. This particular rare soft tissue tumor forms a rather large, slowly growing neoplasm, particularly of the thigh Microscopically nests of cells are surrounded by a reticulin framework Individual cells have prominent nuclei, prominent

nucleoli, and a granular cytoplasm (Fig 936) Mitoses do not occur Multiple nuclei are seen. This tumor invades and metastasizes distantly Smetana believes the tumor is a nonchromaffin paraganglioma and cited Johnson who found non chromaffin paraganglia in the region of Hunter's canal of one patient, a favorite site for this neoplasm. Fisher reported histochemical observations supporting a neural origin. Karnauchow found no paraganglia in the lower limbs at autopsy The treatment is radical excision. Local recurrence and distant metastases may occur many years after the original excision.

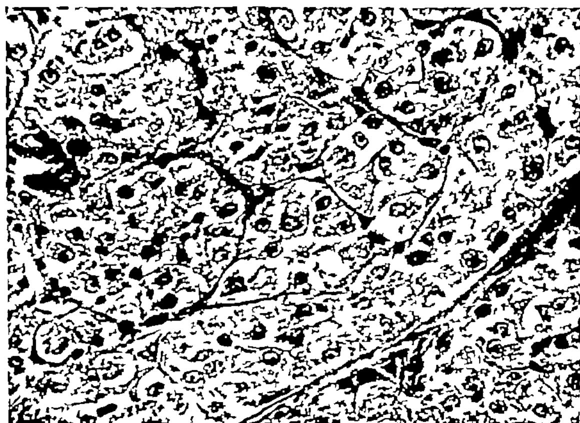


Fig 936 —Photomicrograph of an alveolar soft part sarcoma. Note the arrangement of the cells, the prominent nuclei, prominent nucleoli and granular cytoplasm. (×500) (W U neg 54-4754)

Other Lesions

Further mention should be made of some of the rare tumors of the soft tissue but space does not permit their complete description. It seems certain that with the passage of time further definitive types will be described. The tumors of the soft tissue in children have been particularly mystifying to us. We have seen one example of a *plasma cell tumor* of the soft tissue of the chest (Stout) This tumor later became disseminated. *Primary lymphosarcoma* of soft tissue occurs and at times can be eradicated by surgery or irradiation

Fine reviewed *extraskeletal osteosarcoma* of the soft tissue he was able to find 46 cases. This rare malignant tumor usually contains zones of osteoid formation. It must be differentiated from myositis ossificans (see p 811) *Chondrosarcoma*

also can arise primarily in the soft tissue (Stout). *Ewing's tumor* and *plasma cell myeloma of bone* may penetrate the bone and appear initially as a soft tissue mass. *Metastatic tumors* usually do not mimic soft tissue sarcomas but appear in the subcutaneous tissue.

Pilonidal disease is the term employed for inclusion cysts and secondary sinuses occurring in the subcutaneous tissues over the sacrum. The cysts often become initially infected in young men subject to trauma. Treatment should consist of excision of all chronically infected and sinus-containing tissues as well as all squamous lined cysts and sinuses. The relatively uncomplicated pilonidal cyst may be marsupialized (Buie).

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Chapter 23

PERITONEUM AND RETROPERITONEUM

PERITONEUM

Inflammation

Chemical peritonitis can result from irritation produced by bile, pancreatic juice gastric juice, and barium sulfate (Kay) The peritonitis associated with the intraperitoneal extravasation of barium primarily is the result of the infection accompanying it barium peritonitis practically always follows perforation of the colon during examination of the obstructed bowel Barium particles are doubly refractile and are easily seen with polarized light. Extravasation following injury or disease of the gall bladder, bile ducts, or duodenum causes acute or subacute peritonitis initially in the upper quadrant of the abdomen (Cope) Gastric juice produces a severe peritoneal reaction although it may be sterile because of its hydrochloric acid content The release of pancreatic juice causes fat necrosis. The formation of calcium salts in large areas of fat necrosis may cause hypocalcemia

Bacterial peritonitis may be either primary or secondary The primary form usually is caused by streptococci or pneumococci Aspiration of intra abdominal fluid discloses an inflammatory exudate containing only a single type organism. Large amounts of functional extracellular fluid are lost into the exudate and edema. The losses may be equivalent to those of a burn covering one half to three fourths of the cutaneous surface. Perforation of a viscus such as a colon produces secondary peritonitis. If the fluid is aspirated a mixture of bacterial flora rather than a single organism is found. Tuberculous and actinomycotic peritonitis may occur with

few constitutional symptoms, despite extensive involvement of the peritoneum. These specific mycotic infections are in contrast to primary streptococcal peritonitis which produces maximal constitutional symptoms with minimal gross findings.

Pseudocysts of the peritoneal cavity may occur in conjunction with some inflammatory process such as ulcerative colitis (2 cases) or following appendectomy complicated by abscess (1 case) The large, multilocular cysts have a fibrous tissue wall and are lined by mesothelium (Walker)

Adhesions

Adhesions and the possibility of subsequent intestinal obstruction complicate all intra-abdominal operations. They can be minimized by careful handling of tissues and by reperitonealization where feasible. Intraperitoneal blood clots should be removed. Innumerable agents of every description have been used to prevent adhesions, but none have accomplished this goal. They consist of such substances as sodium citrate heparin, olive oil, liquid paraffin ACTH cortisone pepsin and amniotic fluid. Adhesions become collagenous and strong as the cellularity of their fibrous tissue decreases with maturation Postoperative adhesions are the commonest cause of intestinal obstruction today

Reaction to Talc and Oily Substances

The peritoneum reacts to all foreign substances. A great deal has been written about talcum powder granuloma" of the peritoneum. This foreign body lesion followed the spillage of talc into the peritoneal cavity at operation. Today the hazard of using talc on surgical gloves is recognized and has been abandoned (Eiseman) Talc (hydrated magnesium silicate) causes nodules to form on the peritoneum these nodules are firm and may be mistaken for tuberculosis or metastatic cancer Microscopic examination shows crystals in the tissue which are often better visualized by lowering the condenser of the microscope. They are best seen by polarized light (Fig 937) (German) Mineral oil or paraffin placed in the peritoneal cavity to prevent adhesions may cause nodules which may be mistaken for metastatic carcinoma (Marshall) Frozen section of these nodules is sufficient to make the diagnosis it will show foreign body giant cells, chronic inflammation and macrophages. Similar changes follow rupture of a dermoid type tumor of the ovary in which large amounts of oily material cause a profound peritoneal reaction (Auer)

Primary Tumors

The peritoneum has a great capacity to undergo metaplasia and form papillary projections pseudoacini and even squamous metaplasia (Crome) Cirrhosis of the liver with ascites and chronic inflammation of the peritoneum are associated with *proliferation of mesothelium* (Fig 938) *Primary tumors of the peritoneal cavity* are very rare they may be either benign or malignant (Keasbey) Stout has described a fibrous type mesothelioma of the peritoneal cavity which can be cured by excision. This firm fibrous tumor presents the same bewildering microscopic

picture as the same lesion in the pleural cavity (see Lung, p 189) The proof of origin from mesothelium is based on tissue culture studies rather than the microscopic pattern (Sano) Intermediate forms may occur we have seen localized primary papillary tumors of the peritoneal cavity as well as diffuse forms At times these lesions are resectable The malignant type of mesothelioma may be accompanied by dense fibrous intraperitoneal adhesions with shortening of the

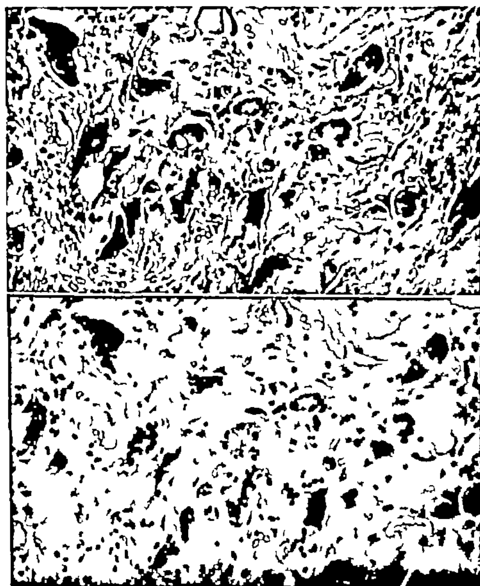


Fig 937—Two photomicrographs, one without polarized light and the other with polarized light. The talc crystals are vividly seen with the polarized light. (Moderate enlargement.) (W U negs. 47 1049 and 47 1050)

mesentery Complete obliteration of the peritoneal cavity may actually develop (Fig 939) The advanced tumor may locally invade the bowel wall the hilum of the spleen the hilum of the liver and the stomach wall. However distant metastases are unusual (Ackerman) The commonest microscopic type of mesothelioma consists of papillary projections with vascularized fibrous cores (Fig 940) Individual cells resemble normal mesothelial cells except that the nucleoli are more

prominent. Mitotic figures are unusual. We have seen two localized mesotheliomas with microscopic patterns similar to synovial sarcoma.

Metastatic Tumors

All types of metastatic tumors involve the peritoneal cavity Their different gross patterns include single, well-defined nodules and diffuse lymphatic permeation. Variations in consistency depend upon their cellularity fibrous tissue content and mucin content. Metastatic carcinoma may simulate very closely primary malig nant mesothelioma we have observed this with metastatic squamous carcinoma

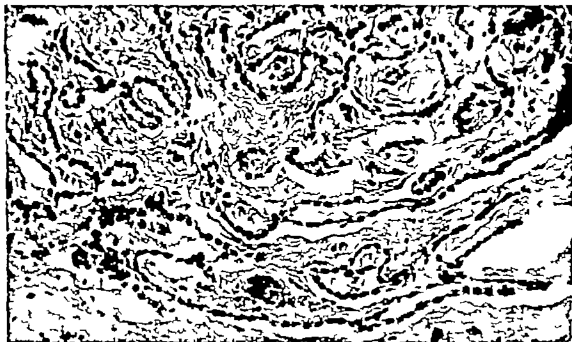


Fig 938 —Photomicrograph of a localized area of proliferation of the mesothelium of the peritoneum. These changes were associated with chronic inflammation. Note the over-production of fibrous tissue and pseudoacini. (×?40) (W U neg. 52-4349)

(Fig 941) Papillary tumors of the ovary can mimic almost exactly the papillary type of mesothelioma (Fig 942) Although primary mesothelioma is rare and metastatic cancer common, the physician should not forget the existence of primary benign mesotheliomas (Wells) because the fibrous type of mesothelioma is curable by excision (Stout) The clinical duration microscopic pattern and evolution of the malignant type of mesothelioma at times leaves no doubt of the specific nature of this entity Willis still believes that primary peritoneal tumors do not exist. We agree that they are rare and that metastatic tumor is often diagnosed erroneously as primary but the collected evidence and the cases we have studied have convinced us that both benign and malignant variants of mesothelioma exist (Ackerman)

Interpretation of Tumor Cells in Peritoneal Fluid

Identification of tumor cells in peritoneal fluid is as difficult as it is in pleural fluid We use two methods of study which complement each other Peritoneal



Fig 939—Gross photograph of a malignant mesothelioma which diffusely involved the peritoneal cavity and which demonstrates prominent fibrosis with shortening of the mesentery (W U neg 49 1666)

Fig 940—Photomicrograph of typical mesothelioma with papillary projections clothing a fibrous tissue core. (×600) (W U neg 49-1793)

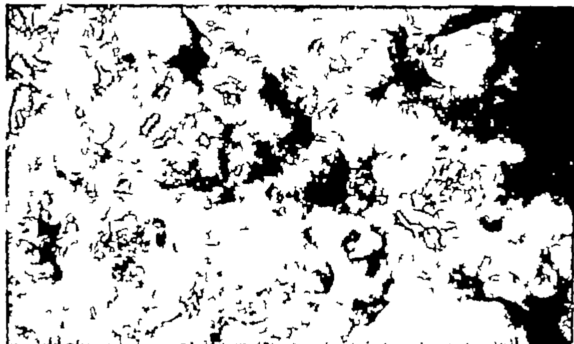


Fig 941—Diffuse involvement of the peritoneum by metastatic squamous carcinoma simulating a primary malignant peritoneal tumor (W U neg 52 383)

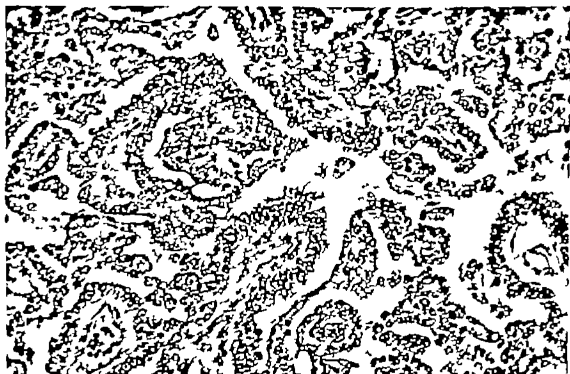


Fig 942.—Photomicrograph of metastatic ovarian cancer of the serous type closely resembling a primary malignant peritoneal tumor (×240) (AFIP 314863)

fluid sediment is fixed, embedded, cut, and stained as in tissue biopsies. These sections have the advantage of concentrating material but some distortion of the cells is inevitable. Fresh smears of the material are stained by the Papanicolaou technique. This allows detailed study of undistorted cells. False positive diagnoses may be made because the mesothelial cells may form pseudoacini which closely resemble adenocarcinoma (Takagi) (Fig 943). Furthermore normal mitotic figures are common. Mesothelial cells also may have multiple nuclei; these may assume a signet ring appearance if the cells contain fat. To be reliable, the diagnosis of cancer cells in fluid must be restricted to those specimens containing abnormal clumps of metastatic cells or numerous abnormal single malignant cells. In both instances the nuclei are large and dense, infrequently atypical mitotic figures are found (Figs. 944-946)

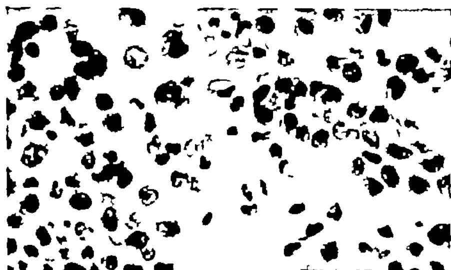


Fig 943.—Photomicrograph of pseudoacini in peritoneal fluid which are easily mistaken for metastatic carcinoma. (×600.) (W U neg 48-4070.)

RETROPERITONEUM

Introduction

The retroperitoneal space is that indefinite area in the lumbar and iliac region which lies between the peritoneum and the posterior wall of the abdominal cavity. It extends from the twelfth rib and the dorsal vertebrae to the base of the sacrum and the iliac crest. The lateral margins correspond to the lateral borders of the quadratus lumbora. The space contains the loose areolar fatty tissue through which pass the ureters, the renal vessels, and the spermatic and ovarian vessels. The retroperitoneal tissue abuts against the inferior vena cava on the right and the aorta on the left. It contains numerous lymph nodes.

The large potential space allows both primary and metastatic tumors to grow silently to large size before clinical signs and symptoms appear. Symptoms are related to pressure phenomena. Objective evidence of retroperitoneal mass can best be demonstrated by retrograde pyelograms and radiographic study of the gastrointestinal tract (Windholz) (Fig. 947)

Nonneoplastic Conditions

Inflammatory processes from the kidney or the pancreas can form a retroperitoneal mass. Retroperitoneal hemorrhage may produce a large hematoma (Leake). We have seen perforation of the biliary system with formation of a bile-containing cystic mass (Cope). Infection can extend from a tuberculous vertebra and form a retroperitoneal cold abscess.

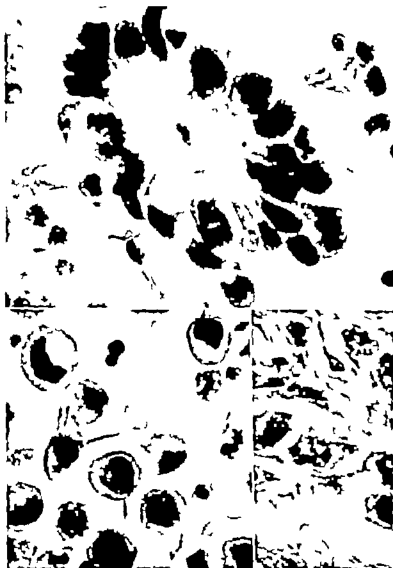


Fig. 944.—Photomicrograph of easily identified metastatic malignant tumor. Note large dense nuclei and atypical mitotic figure in an acinus. (×900.) (W.U. neg. 52-1617.)

Fig. 945.—Photomicrograph of ascitic fluid sediment with numerous tumor cells identified by their dense large atypical appearance. (×900.) (W.U. neg. 52-1621.)

Fig. 946.—Photomicrograph of a microscopic section of this tumor which was primary in the stomach. Note resemblance of the cancer cells in the wall of the stomach to the tumor cells in the ascitic fluid sediment. (×900.) (W.U. neg. 52-1622.)

Primary Tumors

Primary tumors of the retroperitoneal area are relatively rare but are a heterogeneous group. The microscopic recognition of many of these tumors has



Fig 947 —Retrograde pyelogram demonstrating extreme displacement of the kidney and ureter in a patient with a large retroperitoneal tumor (W U neg 49-2913)



Fig. 948 —Large retroperitoneal slimy liposarcoma growing in the region of the kidney (W U neg 50-5055)

been detailed in the chapter on Soft Tissues (see p ??) Liposarcoma is the most common. This tumor usually grows to extremely large size. It is particularly prone to grow in the renal region (Fig 948) It may appear mucoid or resemble brain tissue Many lipomas previously reported in the retroperitoneal area are actually liposarcomas (von Wahlendorf) However a large lipoma does occur retroperitoneally it may appear as multiple tumors and on one occasion it presented initially beneath the inguinal ligament. A leiomyoma from the uterus may grow in the retroperitoneal area. The leiomyosarcoma is the second most common primary sarcoma in this area (Golden) These tumors also become large and cystic degeneration is common in them (Lumb)



Fig 949 —Gross photograph of a paraganglioma arising from a Zuckerkandl body (AFIP 270229)

Rhabdomyosarcomas and angiosarcomas are rare. We have seen only one retroperitoneal rhabdomyosarcoma. Fibrosarcomas are infrequent most of the ones so designated are either lipo- or leiomyosarcomas (Ackerman Warren)

We have rarely seen large retroperitoneal tumors arise from heterotopic cortical adrenal tissue both functioning and nonfunctioning tumors also arise from paraganglionic tissue (Fig 949) A striking example was a 6 cm. functioning retroperitoneal pheochromocytoma which was palpable compression of the tumor caused acute hypertension with systolic pressure above 300. The tumor was quite firm, yellowish-gray and contained areas of hemorrhage. Like most of these, it was perfectly benign (Ganem Cahill) Retroperitoneal teratomas are usually benign but may be malignant The benign types may grow to a large size are often cystic, occur in young children and involve the sacrococcygeal area (Figs 950 and 951)

(Arnheim) Microscopically they contain a variety of well-differentiated elements Often the benign teratoma is considered malignant by the surgeon because of its stubborn adherence to other structures This inflammatory fixation results from the fatty material within the tumor



Fig. 950—Clinical photograph of a baby with a huge cystic benign retroperitoneal teratoma. The teratoma was successfully removed and the child is well (W U neg 52 760)

Fig 951—Gross photograph of a cystic benign teratoma which showed a variety of tissues. (Courtesy Dr R. A. Willis Leeds, England.)

Tumors of nerve sheath origin and from the sympathetic nervous system also arise in the retroperitoneal area (Golden) All types have been reported but are uncommon We have seen a malignant schwannoma of long duration which invaded the bone and distantly metastasized (Figs 952 and 953) We also observed a child



Fig 952.—Roentgenogram of a partially calcified retroperitoneal malignant schwannoma. (W U neg 49-4366)

Fig 953.—Gross photograph of the firm grayish white tumor shown in Fig 952 It directly invaded the vertebra distantly metastasized, and caused death. (W U neg. 49-4225)



Fig. 954.—Gross photograph of a hemorrhagic nodular ganglioneuroblastoma. (Courtesy Dr Malcolm Dockerty Rochester Minn.)



Fig. 955.—Osteolytic destruction of the sacrum by a chordoma. (W U neg 52 2398.)

with a retroperitoneal ganglioneuroblastoma which was removed successfully These lesions often are hemorrhagic, soft, and nodular (Fig 954) A host of other lesions occurring in the retroperitoneal area include various rare tumors such as lymphangioma (Gerster) hemangioma, tumors arising from remnants of renal anlage (Hansmann) enterogenous cysts, and xanthogranuloma (Oberling)



Fig 956.—Chordoma from the intervertebral disc of the sacrum which was felt as a tender extrarectal mass. *This patient remains well over five years after excision.* (Low power) (W U neg. 52 1629)

Inset Typical large cell of a chordoma. Note vacuolated cytoplasm and a well-defined nucleus. (High power)

Metastatic Tumors

Metastatic neoplasms are the most frequent of all malignant retroperitoneal tumors. Origins are Hodgkin's disease, lymphosarcoma and metastatic cancer from tumors of the testis, pancreas cervix endometrium and kidney

Tumors Arising From Notochord—Chordoma

Sacrococcygeal chordomas arise from remnants of the fetal notochord and involve the retroperitoneal space by direct extension They are more frequent in men 40 to 50 years of age but occur at all ages and in both sexes (Gentil) Remnants of notochord lie entirely within the vertebrae and intervertebral discs, rarely they are in the soft tissues close to the sacrum (Berard) Most of the tumors arise from remnants in the bone rather than from those in discs. The craniopharyngeal area is a frequent site of chordoma but the sacrococcygeal zone is the most common. They grow slowly Usually the duration of symptoms before diagnosis is over five years. The tumor invariably destroys a portion of the sacrum by an osteolytic or rarely an osteoblastic process (Fig 955) If the tumor encroaches upon the spine symptoms of spinal cord compression arise The tumor pushes into the retroperitoneal space where it may grow large enough to narrow the lumen of the large bowel or impinge upon the bladder It can be felt as a firm extrarectal mass (Fig 956) These nonencapsulated tumors are soft, gelatinous and contain areas of hemorrhage. In a few instances they may be excised radically but in most instances complete excision is impossible (Dahlin)

Microscopically chordomas closely resemble notochordal tissue as observed in the nucleus pulposus of the intervertebral disc. The neoplasm grows in cords. Alezais believes that the various appearances of chordomas parallel the development of the primitive notochord Individual cells range from small cells with small nuclei and fine nucleoli to extremely large cells The large cells have a vacuolated cytoplasm and infrequently a vacuolated nucleus The largest vacuolated cells have been designated as physaliferous (Fig 956) Some vacuoles contain glycogen (Stewart) Mitotic figures are absent. Areas of cartilage in the neoplasm may be extremely confusing (Mabrey) A few of these tumors metastasize regionally and distantly (Morris)

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Chapter 24

VESSELS

HARVEY R. BUTCHER, JR., M.D.

ARTERIES
VEINS
LYMPHATICS

ARTERIES

ARTERIOSCLEROSIS
- Aneurysm
  - Aortic
  - Popliteal
  - Dissecting
  - Diffuse Arterial Tortuosity and Dilatation
  - Homografts and Synthetic Prostheses
- Major Arterial Occlusive Disease

MESENTERIC VASCULAR OCCLUSION

TRAUMATIC ANEURYSM
- Pulsating Hematoma
- Arteriovenous Fistulas

THROMBOANGIITIS OBLITERANS

POLYARTERITIS NODOSA (NECROTIZING ANGIITIS)

ARTERIOSCLEROSIS

Arteriosclerosis is a generalized progressive arterial disease which causes localized arterial occlusions and aneurysms. Its pathology has gained greater surgical significance in recent years with the development of direct operative therapy for lesions of major arteries. The pathology of arteriosclerosis primarily consists of (1) irregular thickening of the intima caused by lipid deposits, fibrous thickening, and the organization of small surface thrombi secondary to intimal ulceration, (2) degeneration of the media indicated by fragmentation of elastic tissue network, by hyaline, mucinoid, and collagenous degeneration of the smooth muscle and by medial calcification, and (3) adventitial fibrosis and chronic inflammatory cellular infiltration. Arteriosclerosis in an artery presents as an occlusive process when

the disease attacks the intima more rapidly than the media, but as an aneurysm when the reverse is true Both occlusive disease and aneurysm may exist in the same arterial system.

The cause of arteriosclerosis is unknown Factors thought important in its pathogenesis include changes in lipoid metabolism increased intimal permeability to serum lipoprotein complexes the susceptibility of the intima to mechanical injury from flow turbulence at major bifurcations and when hypertension is present, elastic tissue fragmentation and elastase metabolism and thrombosis or disruption of vasa vasorum (National Research Council)

The areas of the arterial tree involved by arteriosclerosis which are commonly and successfully treated surgically have increased rapidly in the past decade so that only occlusions of the smaller peripheral arteries of the extremities and the coronary cerebral, and mesenteric arteries remain The principal manifestations of arteriosclerosis which at present are treated surgically with some success are fusiform and saccular aneurysms of the aorta or other major arteries, dissecting aneurysm, and occlusive disease of the abdominal aorta, the iliofemoral arterial system, and rarely the popliteal subclavian, brachial, and carotid arterial systems.

Aneurysm

Aortic Aneurysm —Aneurysms secondary to arteriosclerosis occur most commonly in the abdominal aorta. Also frequently attacked is the popliteal artery where bilateral aneurysm often develops In these and other arteries which become aneurysmal because of arteriosclerosis the mechanism of development and the pathologic findings are similar Arterial dilatation is likely initiated by a loss of elasticity or weakening of the recoil strength in the arterial wall which results in elongation and tortuosity as well as dilatation. Initially this dilatation is most often fusiform At the same intraluminal pressure tension developed in the arterial wall is greater the larger the diameter of the artery The tendency for dilatation thus increases rapidly after dilatation has begun (de Takats) The progressive dilatation often results in a break in the arterial wall and the development of sacculation of the aneurysm. In other words most arteriosclerotic aneurysms probably begin as fusiform dilatations but with the loss of wall integrity they may become saccular The sacculations nearly always are partially filled with laminated clot which may be the source of emboli into the arteries peripheral to the aneurysm (Fig 957)

The patient with an abdominal aneurysm may be asymptomatic and without clinical findings except for prominent abdominal aortic pulsations. The majority however seek treatment because of dull midabdominal or back pain associated with a pulsating tender epigastric or retroumbilical mass which has enlarged rapidly or has been noted only recently Painful and rapidly enlarging aneurysms will soon rupture if operative therapy is not undertaken. Retroperitoneal hemorrhages from small aneurysms may produce severe back pain with little abdominal symptoms or signs.

Patients with aneurysms of the thoracic aorta survive but a short time without surgical correction. Kampmeir showed the average life expectancy after onset of symptoms to be six to eight months. The prognosis of abdominal aneurysm

appears better than that of the thoracic aorta Estes found that one third of patients with abdominal aortic aneurysm die within one year, usually from rupture He estimated that 90 per cent of patients aged 65 years with untreated abdominal aortic aneurysm would be dead in eight years while only 35 per cent of normal persons of similar age could be expected to die. One may conclude that once aneurysm of the aortic system has been established, its excision and aortic reconstitution are mandatory (DeBakey)



Fig. 937.—Gross specimen of resected abdominal aortic aneurysm which has been transected to show the laminations of the clot (W U neg 57 4850)

Popliteal Artery Aneurysm.—Arteriosclerotic aneurysms of arteries in the extremities are rare except for popliteal aneurysms. The pathologic changes and the progressive enlargement of these aneurysms are similar to those in larger arteries although the rate of progressive dilatation usually is less. Their treatment is essential to avoid acute thrombosis embolic phenomena or rupture as causes of severe peripheral flow deficiency and gangrene. Most patients with popliteal aneurysms are first seen because of these complications. Occasionally such patients seek medical aid because of anterior tibial muscular necrosis. The popliteal arterial

elongation associated with aneurysm formation may kink and occlude the anterior tibial artery as it passes through the interosseous membrane (Julian)

Patients having popliteal aneurysms commonly have multiple aneurysms In 69 patients having 100 popliteal aneurysms, hypertension and occlusive arterial disease were very common (Gifford) Only 3 of these patients were women. Forty of the 69 patients had multiple aneurysms. Thirty-one of them had bilateral popliteal aneurysms and the remaining had aneurysms of arteries other than the popliteal. The most common sites of the second aneurysm in the latter group were the abdominal aorta and the femoral artery Ninety two of the aneurysms were considered purely arteriosclerotic. Syphilis mycotic infections, and trauma entered into the diagnosis of the remaining ones In the absence of extensive gangrene, popliteal aneurysms with or without the presence of complications are best treated by excision of the aneurysm and the insertion of autologous vein grafts or arterial homografts (Julian)

Dissecting Aneurysm.—Dissecting aneurysm of the aorta is associated with a rapidly fatal course in 75 to 90 per cent of cases. Its etiology is related to an underlying degeneration of the elements of the media. The process of dissection most commonly begins in a transverse intimal tear associated with an intimal plaque located either in the ascending aorta or in the upper descending thoracic aorta near the origin of the left subclavian artery Once this tear develops, the intramural layers of the aorta are rapidly separated by the force of the blood entering the wall. The dissection usually involves the entire circumference of the aorta as it progresses distally Perforation often occurs through the adventitia, resulting in early death from hemorrhage into the pericardium or pleural cavity Lower-extremity symptoms and signs of acute occlusion of the abdominal aorta may be prominent because of distal aortic or iliac luminal occlusion by the leading point of the dissection A subacute clinical type characteristically begins abruptly then progresses gradually for several days before rupture and death. Finally a chronic form occurs in a few patients who develop a re-entry site from the dissected passage back into the lumen of the aorta. The occasional long term survivor of dissecting aneurysm is encountered among these persons.

The pathologic and clinical features of dissecting aneurysms have been recognized for many years, but until recently definitive treatment has not existed. The surgical attack upon acute dissecting aneurysm of the aorta has been introduced by DeBakey who has succeeded in salvaging some of these patients. The fundamental principle in the surgical therapy recommended by him is the transection of the lower thoracic aorta and the establishment of a re-entrance site through the intimal layer which had been dissected free by the aneurysmal process. This procedure is particularly applicable when the dissection begins in the ascending aorta. Aortic excision and graft is thought to be superior if the site of beginning dissection is in the upper descending thoracic aorta. Excision was possible in 12 of 16 patients undergoing operation by DeBakey

Diffuse Arterial Tortuosity and Dilatation.—A more or less generalized arterial dilatation and extreme tortuosity occasionally is seen in patients suffering generalized arteriosclerosis. Leriche has reported such instances as dolicho et mega arteria The mechanism of the tortuosity and generalized dilatation is

thought to relate to weakening of the arterial wall but the cause for its generalized nature is not clearly understood We have encountered four such patients, one of which is illustrated (Fig 958) This patient presented with a nontender pulsatile abdominal mass diagnosed initially as an abdominal aortic aneurysm however, be



Fig 958.—Arteriograms of the abdominal aorta and femoral and popliteal arteries illustrating generalized arterial dilatation and tortuosity in a patient who had a pulsating intra-abdominal mass initially diagnosed as aneurysm. (W U neg 57-4727)

cause of the prominence of the femoral arterial pulsation arteriography was performed. There was marked dilatation and tortuosity of the abdominal aorta with bilateral dilatation of the femoral and popliteal arteries. The patient's posterior tibial and dorsalis pedis pulses were normal bilaterally One need know that such arterial dilatation and tortuosity may be mistaken for intra abdominal aneurysm since surgical attack upon such generalized tortuosity is probably not warranted in



Fig. 959 —Photomicrograph of the arterial wall made after amputation for gangrene secondary to embolization from mural thrombi in a dilated and tortuous femoral artery (W U neg. 57 5804)

the absence of complications. Marked enlargement and tortuosity of the femoral arterial tree in one patient was associated with lamellar deposition of thrombotic material along the wall of the tortuous and enlarged artery with maintenance of a lumen through the thrombosis. Embolization resulted in peripheral gangrene requiring amputation. Blood flow from the center of the laminated clot still was brisk at the time of amputation. The arterial wall showed marked loss of normal histologic structure, absence of elastic tissue, and marked fibrosis (Fig 959) In another of these patients marked tortuosity and enlargement of the brachial, axillary and carotid arteries were present without localized aneurysmal formation

Cystic adventitial degeneration of the popliteal artery may cause luminal obstruction. The collection of a jellylike material similar to that seen in ganglions

bulges into the lumen Four such cysts have been reported by Hierton These areas of cystic formation occurred in young males without a history of trauma and without general arterial changes The microscopic structure of the involved arterial segments suggested mucinous degeneration The cysts were lined with flattened cells

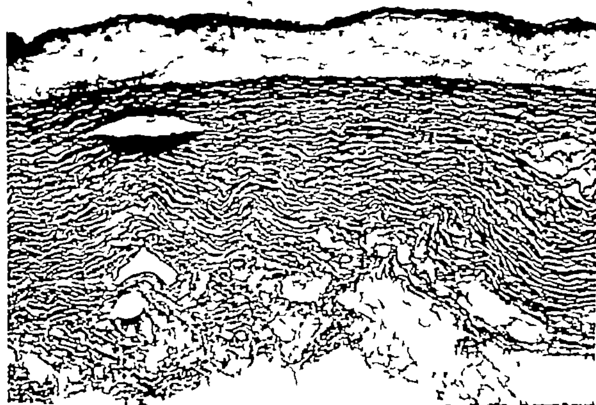


Fig 960—Photomicrograph showing the collagenous encasement of an iliac homograft eighteen months after implantation. (W U neg 57 5807)

Homografts and Synthetic Prostheses—Arteriosclerotic aneurysms of the abdominal aorta, popliteal artery and other major arteries are best treated by excision and replacement of the involved arterial segment by a homograft or a synthetic cloth prosthesis. Although the superiority of one of these is not yet established synthetic cloth prostheses appear less likely to develop degenerative changes after implantation than do homografts (Creech) After implantation, homografts are partially replaced or encased by host collagenous tissue (Fig 960) In a few months they lose much of their elasticity although fragmented elastic tissue is still demonstrable histologically over a year after implantation (Fig 961) The evolution of the intimal surface of both homografts and synthetic cloth prostheses after implantation consists of organization of the fibrin layer initially deposited and the development of a pseudoendothelial lining made of flattened cells. True endothelial ingrowth from the host artery occurs across the suture line for a variable distance usually no more than 1 or 2 cm.

Szilagyi reported late aneurysm formation in 2 of 55 aortic homografts, and tortuous dilatation in 12 of 66 femoral homografts within three years after insertion

Calcification may appear in the wall of homografts after long implantation Implantation of synthetic cloth prostheses is followed by their encasement with collagen and a decline in tensile strength of some of them. Harrison showed that nylon lost 60 to 90 per cent of its strength two years after implantation in dogs.

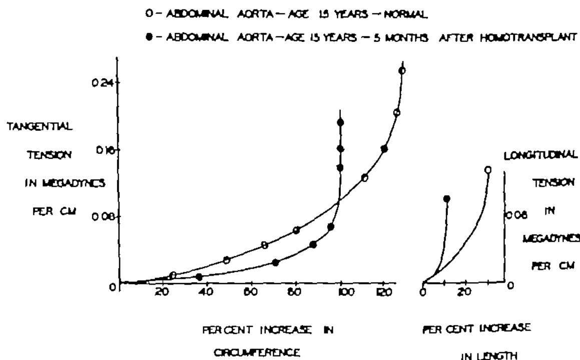


Fig 961 —Graph showing the difference in tension-length relationships of a fresh 15-year-old abdominal aorta and of an abdominal aorta of the same age five months after its use as an aortic substitute. (W U neg. 56-4131) (From Butcher H R. and Newton W T Ann. Surg 148: 1 20 1958)

Dacron, Orlon and Teflon proved much superior in this regard. Controlled experimental hypercholesterolemia in the dog (Creech) and rabbit (Fisher) produced atherosclerotic changes in lyophilized homografts which were greater than those in the host arteries. Creech also found that hyperlipemia in the dog produced no atherosclerotic changes in implanted nylon prostheses. Although homografts have been used extensively to successfully replace diseased larger arteries, it would appear that the newer synthetic prostheses are superior (Crawford) In some instances however homografts have technical advantages over synthetic prostheses which relate to ease of suture, pliability and anatomical structure. For example homografts for replacement of uncommon aneurysms of the thoracicoabdominal aorta involving the celiac, superior mesenteric, and renal arteries are technically superior because a homograft of human aorta with anatomically similar arterial branches is readily available (DeBakey) Endoaneurysmorraphy and the intra aneurysmal wiring are no longer indicated in the treatment of aneurysm.

Major Arterial Occlusive Disease

Thrombotic occlusions of the major arteries are associated with arteriosclerotic changes such as calcification, atheromatosis, and ulceration of the intima. The occlusive process is often insidious although final thrombotic obliteration of the lumen is occasionally quite rapid and may be clinically indistinguishable from embolization. Indeed, the differentiation of the two pathologically and at operation is quite difficult in the older age groups where arteriosclerosis of the abdominal aorta is nearly universal The process of occlusion probably begins in the iliac arteries near the aortic bifurcation from which thrombus formation propagates cephalad in the aorta occasionally to the level of the renal arteries. The syndrome



Fig. 962.—Gross specimen removed from a patient with thrombotic occlusion of the distal abdominal aorta and common iliac arteries (Leriche syndrome) (W U neg 54-5749)

of distal aortic thrombosis (Leriche syndrome) manifests itself with an insidious onset and gradual progression of symptoms of pain and easy fatigability in the legs hips, and back intermittent claudication and sexual impotence (Fig 962) Arterial insufficiency in the lower extremities usually is manifested clinically by absence of pulses below the inguinal ligaments If the process is partial weak pulsations may be felt or a characteristic systolic murmur heard over the abdominal aorta. Despite the presence of intermittent claudication and the absence of pulses many of these patients are found by arteriography to have near normal distal arteries. This patency of the peripheral arteries probably is responsible for the relative absence of muscular atrophy or of atrophy of skin appendages in the legs and feet of these patients despite their symptoms of peripheral blood flow insufficiency and lack of pulses.

Arteriosclerotic occlusive disease also commonly involves other major arterial bifurcations in the lower extremity such as those of the common iliac and common femoral arteries. In the latter instance the intimal disease and thrombosis occur frequently in the external femoral artery just distal to the bifurcation. Other arterial segments in the lower extremity prone to early thrombotic occlusion are those associated with some degree of fascial fixation. Such areas exist (1) in the external iliac artery behind the inguinal ligament (2) in the superficial femoral artery as it passes through the fascial ring beneath the adductor magnus tendon and (3) in the anterior tibial artery where it passes through the interosseous membrane.

Although arteriosclerosis is a generalized arterial disease the tendency for occlusive complications to develop early in its evolution at the sites just noted makes possible the successful treatment of patients with marked peripheral blood flow deficiency Surgical correction of the obstructive disease however may only temporarily improve the peripheral blood flow because of the progressive nature of generalized arteriosclerosis.

The treatment of major arterial occlusive disease is being undertaken by surgeons today using two general methods (1) the use of arterial homografts or synthetic arterial prostheses and (2) endarterectomy (intimectomy) The relative efficacy of these two methods has not been determined. Successful results in 85 to 95 per cent of patients with occlusions of the aortic and iliac arteries have been reported by both methods of treatment (DeBakey Cannon, Julian Wylie) Postoperative aneurysm formation and vascular thrombosis have been reported using both methods. Data which will allow one to analyze the relative frequency of these complications are not available. The end results of both resection with arterial replacement and endarterectomy may well prove them to be of equal worth The correction of femoral occlusive disease with homografts either end to end or by the bypass technique (Linton) has proved less beneficial than grafts in larger arteries approximately 70 per cent of the femoral grafts develop late thrombosis (Warren) The incidence of late failure of both endarterectomy and arterial grafting procedures will likely always be higher in the smaller femoral artery than in the aorta and iliac arteries. Results after femoral endarterectomy reported by Cannon indicate approximately 50 per cent of patients maintaining good results six months to two years after operation

The histologic changes encountered after homograft implantation consist of the development of a thin layer of fibrin over the intimal surface which is rapidly replaced by a smooth pseudoendothelium. The fibrin layer is soon replaced by fibrous tissue and collagen which varies in thickness. There is rapid degeneration of the media so that with the passage of a few months it usually is quite thin and amorphous and the elastic tissue is fragmented in some grafts the elastic tissue remains and is still only partially fragmented after two to three years (Creech) On the adventitial surface of the graft there is laid down a layer of fibrous tissue and collagen of varying thickness, which in some grafts appears to invade and replace a portion of the media. If the arterial outflow tract allows rapid transit of blood through the graft, early thrombotic occlusion of the graft is unlikely in spite of the deposition of fibrin over its intimal surface.

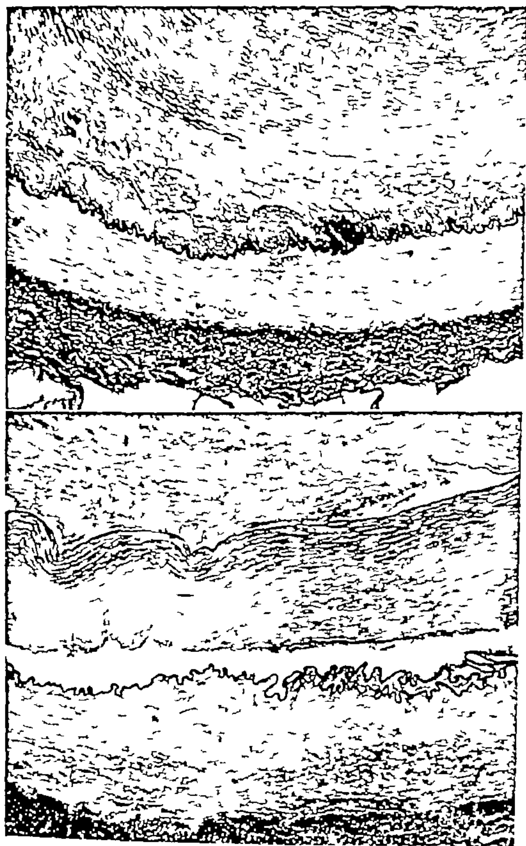


Fig 963 —Photomicrographs showing the result of an endarterectomy performed upon an occluded *femoral* artery removed at autopsy The vessel was transected and the section above made from one of the cut ends. The tissue section shown below was made from the other cut end after *simple* wire loop endarterectomy The freed intimal core was left in situ in order to demonstrate the plane of cleavage developed. (W U neg 57 5915A.)

Thromboendarterectomy of major arteries is a technique in which the diseased intima and thrombotic material filling the lumen is dissected from the inner portion of the media in a smooth and uniform manner so that the remaining adventitia and media of the artery can continue to conduct blood (Fig 963) The remaining arterial tube is lined rapidly by a fibrinoid layer which develops a pseudoendothelial surface similar to that lining an implanted homograft. Likewise, early thrombosis does not occur in these segments if the transit time of the blood through them is rapid. Endarterectomized arterial segments examined months after the operative procedure show a fibrous type of intima with an endothelium like covering and preservation of the remaining media and elastic tissue (Barker) Extensive medial calcification of the Mönckeberg type may prove a contraindication to endarterectomy

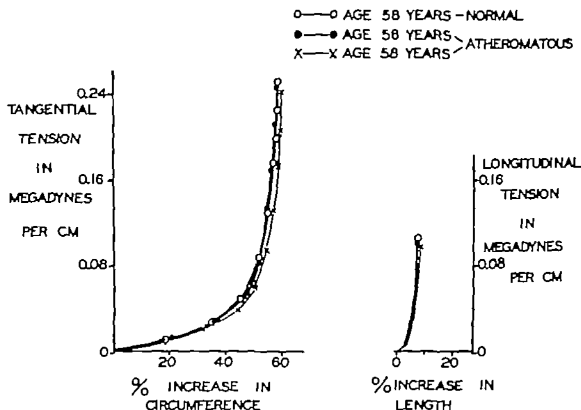


Fig 964—Graph showing no difference between the tension-length relationships of normal and atheromatous abdominal aortae of similar age. (From Butcher H. R., and Newton, W T Ann. Surg. 148: 1-20 1958)

Studies of the elastic properties of normal human arteries and arteriosclerotic ones from autopsies of patients of the same age have shown insignificant variations of elasticity coefficients between the two Such a comparison between normal and arteriosclerotic abdominal aortas is shown in Fig 964 The progressive encasement of synthetic prostheses with collagen and the similar encasement and invasion of fibrous tissue into the wall of homografts are associated with a reduction in the elastic properties of the implants their distensibility becomes much less after im-

plantation (Butcher) (Fig 965) Studies of both cloth prostheses and of homografts at varying times after implantation indicate that the end result is a collagen like tube through which the blood flows The response of the wall of the graft to distention is no longer that of the adjacent host vessels



Fig. 965 —Photomicrograph showing a nylon arterial prosthesis one year after implantation. (W U neg 57 5805)

MESENTERIC VASCULAR OCCLUSION

Mesenteric vascular occlusion may originate in veins or arteries rarely occlusion of both occurs simultaneously Reports in recent years indicate arterial occlusion to be much the commonest (62 per cent of cases) (Wilson) After the initiation of arterial or venous thrombosis, hemorrhagic infarction of the intestine and its mesentery develop if the process is rapid in onset and extensive. Johnson reported that venous mesenteric thrombosis often is associated with infection and cancer this association was present in 25 per cent of his 99 cases However infection and cancer per se were not directly related to the mesenteric venous thrombosis. The true correlation in the 25 per cent having infection and cancer was between portal venous obstruction and mesenteric thrombosis. The relative reduction in frequency of mesenteric venous occlusion in recent years has been attributed by Wilson to antibiotic control of many intra abdominal infections. In the past sepsis was thought to cause the majority of the mesenteric venous occlusions. Occlusion of the mesenteric arterial system may be caused by emboli from thrombi in an arteriosclerotic aorta, from a fibrillating auricle, or finally from a

mural thrombus secondary to myocardial infarction Mesenteric arterial occlusion also may follow arteriosclerotic change in the superior mesenteric artery with local thrombosis and such rare conditions as polyarteritis or septic arteritis.

Infarction of the small intestine or colon perforation and peritonitis do not always follow mesenteric vascular occlusion either arterial or venous. Johnson reported the presence of infarction in only 52 of 99 patients found to have mesenteric vascular occlusions post mortem. Infarction of the bowel depends upon the location the extent of the occlusion, the rapidity of its onset, and the state of the collateral circulation as well as the general physical condition of the patient. Patients with cirrhosis of the liver and portal hypertension commonly have episodes of cramping abdominal pain associated with low-grade fever and moderate leukocytosis which gradually recede. Several such episodes may take place before sufficient amount of the portal venous system is occluded to cause the clinical picture of intra abdominal catastrophe The clinical diagnosis of mesenteric vascular thrombosis is at times difficult because the patient does not present the classical severe abdominal pain distention, nausea, vomiting leukocytosis, and shock. Such a picture depends upon a massive sudden occlusion of the superior mesenteric artery or vein.

Acute occlusion of mesenteric arteries produces bowel necrosis without the early marked hypovolemic disturbances seen with extensive venous thrombosis. Bloody diarrhea is less common in arterial than in venous occlusions although abdominal pain generally is more prominent with arterial ones. If the occlusion is sufficiently extensive to cause gangrene of the bowel death from peritonitis follows if the bowel is not resected. A hypovolemic death in less than twenty four hours however is often the outcome in the presence of massive venous occlusion (Allen) Of the two types of occlusion arterial embolic occlusion is more likely to be amenable to successful treatment than is venous thrombosis. The treatment of both conditions consists primarily of early abdominal exploration and resection of nonviable bowel. The determination of viability at laparotomy may be quite difficult. The extent of small bowel resection compatible with subsequent life has been shown by experience to be as much as three fourths of the intestine in some patients. Embolectomy to date has but rarely remedied occlusion of the superior mesenteric artery however because of the serious prognosis associated with extensive small intestinal and colonic resection this procedure probably should be attempted more often (Kleitsch) Postoperative anticoagulant therapy is considered of value in the management of acute vascular occlusion in the mesentery

We have encountered three patients in whom it appears that vascular impairment of a segment of small intestine was followed by pathologic changes and clinical findings which were quite similar to those seen in regional ileitis. One patient developed cramping abdominal pain and tenderness in the right lower quadrant approximately one month after having had coronary thrombosis. A diagnosis of appendicitis was made and the abdomen was explored The terminal ileum was described as being edematous and blue in color it was not removed. Following the operation the patient entered Barnes Hospital with fever leukocytosis, and guaiac positive stools. Roentgenograms of the small intestine were interpreted

as showing cicatrizing enteritis Symptoms persisted for approximately six weeks, at which time the patient died of pulmonary edema Pathologic examination showed approximately 40 cm of the terminal ileum to have submucosal thickening mucosal ulceration and a few giant cells A major branch of the superior mesenteric artery contained organized thrombus The lymph nodes contained inflammatory cells but no granulomas (Pope)

TRAUMATIC ANEURYSM

Pulsating Hematoma

The pulsating hematoma or false aneurysm results from a small perforation in the artery produced usually by a sharp instrument or small missile. The defect is only a few millimeters in diameter but is sufficiently large to allow the escape of blood into the immediately surrounding tissues Cohen has emphasized the role of the adventitial layer in the development of the aneurysmal sac because of its tendency to seal off the defect in the arterial wall Of equal importance is the nature of the surrounding tissue and the strength of its fascial structures When strong fascial surroundings are absent the rate of aneurysmal enlargement is quite rapid it is slower when the area of injury is within a circumscribed fascial channel such as Hunter's canal. The blood collects about the defect in the artery until the pressure within the hematoma approaches the mean blood pressure. Enlargement of the hematoma then slows because blood returns to the arterial lumen during diastole. It is this situation that produces the characteristic to-and fro murmur heard over the pulsating hematoma. This murmur has a rather harsh systolic component and a softer diastolic component the murmur is not constant as is the murmur of arteriovenous fistula. The walls of the pulsating hematoma contain varying amounts of laminated clot, which in turn is surrounded by a rather dense fibrous tissue reaction The operative treatment of pulsating hematoma often is not difficult. Usually the arterial wall defect can be closed by simple suture after evacuation of the hematoma and excision of the fibrotic aneurysmal sac. Occasionally however the arterial defect requires replacement by homograft or other arterial prosthesis (Shumacker) These lesions should be treated immediately upon diagnosis in order to prevent continued enlargement, pain upon compression of adjacent nerves and other structures and ischemia of the tissues peripheral to it (Julian) Since ligation of the afflicted artery if it be a major one is no longer the treatment of choice waiting for collateral vessels to develop is not indicated

Arteriovenous Fistulas

Arteriovenous fistulas are seen most commonly during times of war and are produced in a manner quite similar to that of traumatic aneurysm however in this instance the perforating injury has involved both the artery and the adjacent vein. Such an injury usually results in a pulsating hematoma which communicates both with the arterial and venous lumina. Following trauma the fistula may be established almost immediately however the communication between the arterial and venous systems is frequently delayed until the wound is partially organized and the thrombus in the hematoma surrounding the artery and vein is partially

absorbed. Most patients present with a pulsating mass in the region of injury which can be differentiated from simple pulsating hematoma in several ways. The murmur over the pulsating region is usually continuous because of a continuous flow of arterial blood into the vein. In other words, during diastole the pressure in the pulsating hematoma about the arteriovenous communication is never sufficient to produce reversal of blood flow In some slowly developing long standing arteriovenous communications in the absence of a pulsating hematoma a massive sacculation of the adjacent vein may slowly develop This is illustrated by the following case history

A 68-year-old Negro woman suffered a shotgun wound of the right thigh at the age of 38 A mass was first noted on the medial side of the right knee twenty-one years later The mass slowly enlarged over the intervening time until it reached sufficient size to interfere with walking (Fig 966) The large sacculation associated with the arteriovenous fistula in this woman contained no laminated clots but was covered by an endothelium-like surface. The popliteal vein entered the sacculation from below and the femoral vein left it above. There was a 6 mm. communication between the femoral artery and the venous sac. The arteriogram showed marked femoral arterial dilatation a characteristic finding in long-standing arteriovenous fistula. Branham's sign was positive occlusion of the femoral artery produced a sudden slowing of the pulse. This patient also exhibited significant cardiac enlargement but had not had difficulty with cardiac failure. Treatment consisted of ligation of the popliteal and the femoral veins near their communication with the aneurysmal sac and suture of the 6 mm. arterial wall defect. There was rapid decrease in cardiac size following the operation (Fig. 966) The diameter of the femoral artery and the prominence of its pulsation decreased in subsequent months.

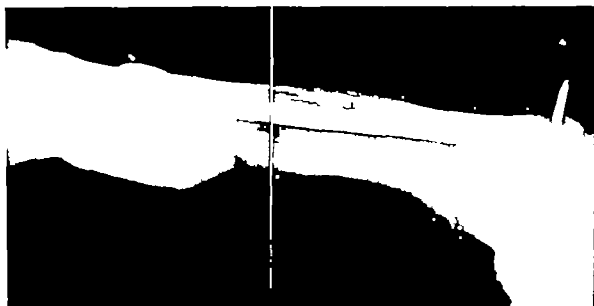
Patients with arteriovenous fistula usually show venous dilatation about and peripheral to the fistula as well as increased skin temperature in the area of the fistula. Despite increased temperature near the lesion, the extremity peripheral to it is usually cooler than normal since the actual peripheral blood flow is less. When arteriovenous fistulas develop between smaller arteries and veins, the sac may be excised and the vessels ligated without difficulty Those involving the larger arteries such as the femoral or axillary require the maintenance of arterial continuity Some type of arterial substitution may be necessary occasionally in larger arteriovenous aneurysms, although transvenous closure of the defect in the arterial wall usually can be satisfactorily accomplished

The dilatation of the major artery entering an arteriovenous fistula of long standing may be marked and the degenerative changes in the arterial wall may be extensive (Holman) These changes consist of atherosclerosis, calcification disruption of the elastic tissue network and fibrosis. If the degeneration is sufficiently advanced it is irreversible In such arteries, aneurysms may develop despite the cure of the arteriovenous fistula. The dilatation of the artery entering the arteriovenous fistula is thought to result from the increased flow of blood through it. Arteriovenous fistulas are associated with increase in cardiac output pulse rate, and blood volume which may lead to congestive heart failure. Such systemic results rarely if ever develop from a single congenital arteriovenous fistula with the exception of those which appear in the pulmonary tree. Congenital arteriovenous fistulas usually present as tumefactions containing many relatively small arteries and veins surrounded by moderately large amounts of fibrous tissue Their treatment is primarily excisional (de Takats)

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans is a rare thrombotic and inflammatory disease of arteries and veins of unknown etiology which has no single diagnostic, clinical or pathologic finding. Its inflammatory component may involve entire neurovascular bundles. Although it is a generalized vascular disease the involvement of the

A





B *C*

Fig 966.—*A* Arteriogram above shows the markedly enlarged femoral artery entering the region of arterial venous fistula. *B* Photograph of the chest examination before correction of the arteriovenous fistula. *C* Roentgenogram of the chest in the same patient five days after operation. (W U neg 57 980)

arteries of the lower extremities is usually most advanced, and the resultant flow deficiency is the common cause for the patient's seeking therapy The onset of the condition occurs most often in men 20 to 35 years of age. In them its onset may be heralded by superficial migratory acute thrombophlebitis which is precipitated by undue exertion or exposure to cold Study of biopsies of such involved veins shows the histologic changes associated with acute intravascular thrombosis. Pathologic involvement in the arterial tree is segmental and usually is present primarily in the smaller arteries. Microscopic examination of early arterial lesions shows panarteritis, periarteritis and thrombosis. Endothelial proliferation and



Fig 967 —Photomicrograph showing the cellular organization of the occluding thrombus with small recanalizing channels thought to be compatible with Buerger's disease. Note the absence of calcification (W U neg 58-643A.)

periarterial fibrosis soon become prominent. The inflammatory process attacks the entire thickness of the vessel wall and perivascular tissues where nerves are in close proximity to the vascular tree it involves the perineural stroma. Extension of the inflammatory process about peripheral sensory nerves may be in part responsible for the severe pain so common in afflicted extremities. In other words, neuritis as well as vascular ischemia may contribute to peripheral pain in these patients. Calcification in the arterial wall is absent. Arterial calcification on x ray

examination indicates arteriosclerosis The arterial and venous thrombosis associated with the angiitic process becomes partially recanalized Cellularity of the organizing fibrous tissue replacing the thrombus often is prominent. Recanalization of thrombi is incomplete and is characterized by numerous small vascular channels passing through the remaining fibrous tissue (Fig 967) The pathologic process ascribed to Buerger's disease is difficult if not impossible, to differentiate microscopically from inflammatory and fibrotic changes which may accompany arteriosclerotic thromboses (Kelly) There is no conclusive evidence of a primary angiitic etiology the basic lesion seemed to be arterial thrombosis in the 10 cases studied by Gore.

The vascular process tends generally to be progressive, but in some instances the acute manifestations seem to subside particularly in patients who cease the use of tobacco. Little long term improvement is attained with or without sympathectomy so long as patients use tobacco (Selbert) In many of those who stop tobacco the progressive vascular occlusion appears to cease but in nearly all who continue using tobacco the disease progresses eventually to gangrene. Treatment is symptomatic and includes the control of pain the avoidance of tobacco and cleanliness of the extremity Late in the disease amputations may be necessary sympathectomy may benefit the patient with a cold temperature sensitive foot or hand or with peripheral gangrenous ulcers

The death of persons with Buerger's disease may follow complications attending gangrene of the extremities. However many patients with this affliction die of myocardial infarction renal insufficiency occlusions of mesenteric vessels and strokes. Buerger's disease should be looked upon as a rare generalized vascular disease more often attacking the smaller arteries than the aorta and its major branches. Its cause is unknown, its pathologic delineation vague, and its angiographic separation from arteriosclerosis not yet possible. With the routine use of arteriography in patients with peripheral arterial insufficiency the clinical diagnosis of thromboangiitis obliterans now is rarely made Whether it can be differentiated from arteriosclerotic thrombotic disease is doubtful (Wessler Theis) We have found it extremely difficult to identify specifically the existence of the entity Buerger's disease No good examples have been found in the pathologic files at the Jewish Hospital, St. Louis (Hasson) During the past five years only three cases which could be classified as thromboangiitis obliterans have been seen. It is obvious that this process requires pathologic re-evaluation it may be only a manifestation of embolization or thrombosis associated with recanalization (Hershey)

POLYARTERITIS NODOSA (NECROTIZING ANGIITIS)

Polyarteritis nodosa in the past was considered a rare disease and was characterized at autopsy by visible nodular lesions at the points of branching of small and medium-sized muscular arteries. This term has come to include a variety of lesions, many of which are seen only microscopically Zeek has proposed the term necrotizing angiitis which would include hypersensitivity angiitis allergic granulomatous angiitis rheumatic arteritis polyarteritis nodosa and temporal arteritis (see Central Nervous System) As polyarteritis nodosa is often an expression of hypersensitivity we are seeing more and more examples of this entity The con

dition should be suspected clinically if there is a history suggesting hypersensitivity with fever, eosinophilia, and involvement of many organ systems. Infrequently there may be skin manifestations. A muscle biopsy occasionally will show definitive findings. A biopsy is most rewarding in the presence of a nodule. In a group of cases seen at the Mayo Clinic in which the diagnosis was proved 35 per cent had a positive biopsy diagnosis (Maxeiner) If the diagnosis is proved, usually small vessels are involved with thrombosis, inflammation and eccentric destruction of arterial walls (Fig 968) Rarely organs such as the gall bladder, appendix, or colon may show unsuspected lesions typical of polyarteritis Involvement of the stomach and pancreas also has been observed at the Barnes Hospital



Fig 968 —Polyarteritis involving small vessel of the subcutaneous tissue. Note thrombosis, inflammation, and eccentric involvement. (×340) (W U neg 51-6019)

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VEINS

ACUTE THROMBOPHLEBITIS—THROMBOEMBOLISM
STASIS ULCERS
VARICOSE VEINS

ACUTE THROMBOPHLEBITIS—THROMBOEMBOLISM

Thrombophlebitis is a thrombotic disease of veins accompanied by varying degrees of inflammation The venous wall is edematous the intima irregularly ulcerated, and the media infiltrated with chronic inflammatory cells (Fig 969) As the acute inflammatory phase of the disease subsides varying amounts of fibrous tissue and collagen are deposited in the adventitia and media. During the acute phase the thrombus becomes attached more or less firmly to the denuded intima The process of thrombophlebitis is associated with edema of the part, which may be minimal or marked. When there is but little edema and few or no clinical signs of acute inflammation in the extremity the venous thrombosis has been termed phlebothrombosis or bland noninflammatory venous thrombosis (Oschner) The noninflammatory type of thrombophlebitis is probably more frequently associated with pulmonary emboli than is thrombophlebitis associated with more marked signs of inflammation. However the rigid separation of phlebothrombosis from thrombophlebitis is not possible pathologically or practical clinically these conditions are merely different degrees of the same process.

Thrombophlebitis may involve only the superficial veins such as the saphenous vein. The vein is acutely inflamed tender, and the overlying skin is usually red. When such thrombosis of the superficial veins occurs, there is usually little edema however thrombophlebitic edema may develop with marked rapidity and be of great volume if the process extends into the deep venous system. Rapid shifts of extracellular fluid into the leg may be sufficiently massive to cause shock (Moyer) In such instances the extremity may become so swollen that cutaneous blebs develop followed by cutaneous necrosis (phlegmasia cerulea dolens) Thrombophlebitis of this severity however is uncommon the usual postoperative or post traumatic acute thrombophlebitis causes initially a painful tender swollen, cool and mottled or grayish white extremity

Purulent or septic thrombophlebitis occasionally is seen in association with abscess or other infection usually occurring in the peritoneal cavity or pelvis. Purulent thrombophlebitis at any location is associated with marked chills and high fever because of the bacteremia arising from the infected intravascular thrombus.

Pulmonary embolism is often thought to be primarily a complication of some surgical procedure or trauma such as fracture particularly of the lower extremity

but the incidence of this complication is as high on medical as on surgical services (McCartney) Some of the factors thought to favor intravenous thrombosis and subsequent pulmonary embolism are cardiac disease, venous stasis from any cause, infection in the immediate area of veins, trauma, spasm of vessels, intimal injury, increased ability of the blood to coagulate, and immobilization of the limbs how ever the basic etiology or initiating mechanisms are not known. The importance of endothelial surface injury and defects has been emphasized by Samuels, using the technique devised by O'Neill. Pulmonary embolism is seen in all forms of



Fig 969—Photomicrograph showing acute venous thrombosis accompanied by an inflammatory cellular infiltration containing giant cells. (W U neg 58-6275)

thrombophlebitis Sudden massive pulmonary emboli commonly occur however in patients without prior symptoms or signs of peripheral thrombophlebitis.

The greatest percentage of thrombi resulting in pulmonary embolization are thought to originate in the veins of the lower extremity Rössle found that 27 per cent of patients over twenty years of age harbored thrombi in the veins of the calf at autopsy Hunter's study confirmed these observations and indicated that the thrombosis occurred in over 50 per cent of middle aged or older people confined to bed McLachlin has stressed the finding of intravascular thromboses arising in relationship to the valve pocket. In 100 complete dissections of the veins of the pelvis and lower extremities he showed gross venous thrombi in 34 per cent and in over one half of these there were pulmonary emboli (Fig 970) In his series the thrombi found in 34 patients totaled 76 there were 6 thrombi in the pelvic veins,

49 in the thigh veins and 21 in the leg veins In other words he found that 75 per cent of the venous thrombi arose in the veins of the thigh and pelvis and 25 per cent in the smaller veins of the calf and feet Ninety two per cent of the venous thrombi arose in the lower extremities Crane concludes that the evaluation of all data available concerning the origin of fatal pulmonary emboli indicates approximately 85 per cent of them arise in the legs This figure may well be 90 per cent in postsurgical patients and 80 per cent in cardiac or medical patients

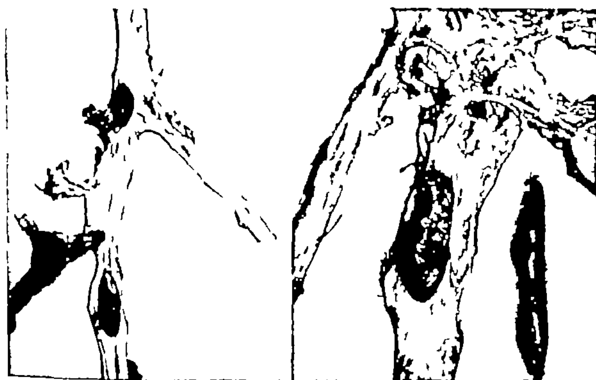


Fig. 970—Left, A case of multiple venous thrombi. The lower one is lying in a valve pocket at the upper end of the superficial femoral vein. The middle one on the left is lying in the proximal end of the profunda femoris vein, while the upper thrombus is lying in the common femoral vein at the junction of the long saphenous vein.

Right, A thrombus arising in a valve pocket at the upper end of the superficial femoral vein. The lines of Zahn are clearly seen. Postmortem clot is shown for comparison.

(From McLachlin, J., and Paterson J C. Surg Gynec. & Obst. 93 1-8 1951)

STASIS ULCERS

The chief immediate complication of thrombophlebitis is pulmonary embolus the principal late one is stasis ulceration The treatment of acute thrombophlebitis attempts to limit the extension of the process and to prevent pulmonary embolization. Elevation rest with the maintenance of good hydration elastic support, and possibly anticoagulant therapy are the initial measures. Ligation of the venous system above the area of intravascular clotting is occasionally indicated when these measures fail to prevent pulmonary embolus. As the acute phase of the disease subsides, measures must be taken to avoid later stasis disease in the lower extremity The use of elastic supports to help control any dependent edema in the extremity is imperative and may be required for many months or years. With the passage of time collateral venous channels may develop and communicate with the superficial venous systems secondary superficial varicosities result Re

but the incidence of this complication is as high on medical as on surgical services (McCartney) Some of the factors thought to favor intravenous thrombosis and subsequent pulmonary embolism are cardiac disease, venous stasis from any cause, infection in the immediate area of veins trauma, spasm of vessels, intimal injury increased ability of the blood to coagulate, and immobilization of the limbs, however the basic etiology or initiating mechanisms are not known. The importance of endothelial surface injury and defects has been emphasized by Samuels, using the technique devised by O'Neill. Pulmonary embolism is seen in all forms of



Fig 969 —Photomicrograph showing acute venous thrombosis accompanied by an inflammatory cellular infiltration containing giant cells. (W U neg 58-6275)

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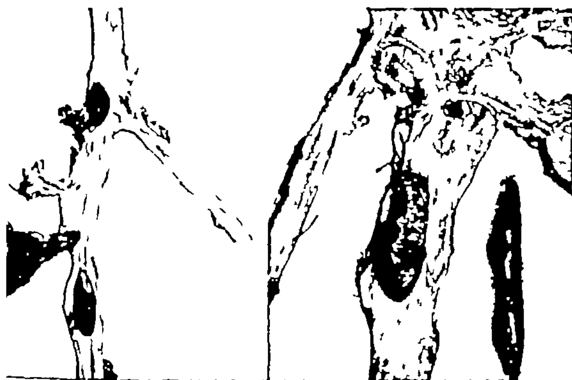


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canalization of the major deep veins usually is associated with this process. Any significant varicosities in the postphlebitic extremity should be removed. For reasons not clearly understood the prevention and control of stasis ulceration is quite difficult in the presence of subcutaneous varicosities. The preventive measures directed toward control of dependent edema often are not carried out by patients suffering from thrombophlebitis so that after several years there develop cutaneous pigmentation, brawny edema, dermal and subcutaneous fibrosis, extensive secondary varicosities and ulceration of the skin in the lower one third of the leg. Although stasis ulcers are seen in patients who have a history of past thrombophlebitis, such a history commonly is absent (only 50 per cent of the patients seen in the Washington University Clinics have such a history). Even in patients with prior thrombophlebitis the exact pathogenesis of the process leading to ulceration is unknown. The diagnosis of stasis disease is usually not difficult, only occasionally are ulceration, pigmentation and surrounding fibrosis confused with other forms of ulceration. Prior to extensive treatment of a patient with advanced chronic leg ulcer, careful evaluation of the arterial blood supply should be made. Any significant arterial flow deficiency will likely result in failure of the surgical therapy for ulceration. Correction of major arterial occlusion should be made when possible before treatment of the stasis ulcer in those patients in whom both are present. Obviously the other rare causes of ulceration such as specific infections and neoplasms must be excluded. All ulcers should be cultured and any unusual appearing ones biopsied before excisional therapy is undertaken.

If ulceration has not yet appeared or is not extensive or chronic in nature, the total removal of the varicose veins with ligation of perforating veins may control the process. If stasis ulceration is extensive, chronic, and long standing it is best treated by excision and stripping of all superficial varicosities of the extremity after high ligation and division of the saphena magna and its tributaries at the saphenal femoral junction. The ulcer and its base should be excised down to normal tissue with removal of all the inelastic thickened skin and fascia about it. The cutaneous-fascial defect should then be covered with a partial thickness cutaneous autograft (Moyer). The results of this form of therapy at Barnes Hospital are shown in Table 44. The extent of excision often required for advanced stasis ulceration

TABLE 44 RESULTS OF EXCISIONAL THERAPY IN PATIENTS WITH CHRONIC STASIS ULCER

YEARS AFTER TREATMENT	PATIENTS AT RISK	PATIENTS WITH ULCER	PATIENTS WITHOUT ULCER
1	78	18	60 (77%)
2	59	13	46 (78%)
3	50	10	40 (80%)
4	36	7	29 (80%)
5	21	4	17 (80%)

is shown in Fig 971. In most of these advanced cases the depth of the excision should include the fascia overlying the muscle, for in the presence of long-standing stasis ulcers the fascial fibrosis and thickening is quite extensive. This also facilitates ligation of the perforating veins which are invariably present beneath the area of stasis fibrosis.



Fig 971 —*A* Photograph showing a long-standing chronic stasis ulcer refractory to conservative management. *B* Fibrotic skin subcutaneous tissue and fascia have been widely excised periosteum and peritendineum were not removed *C* Photograph of the extremity two years after operation (W U neg 57 5074)

VARICOSE VEINS

Varicose veins occur more frequently in women than in men. Their incidence is much higher in obese women particularly those who have had several pregnancies. Women who develop varicosities after pregnancy may have varicosities secondary to deep venous thrombosis. Larson reported that 213 out of 491 patients (43 per cent) had a definite family history of varicose veins indicating some hereditary disposition. The superficial veins of the leg become dilated and tortuous and lose valvular function. Microscopically there is replacement of the wall by fibrous tissue and thinning of the muscle in most areas, but in some there is focal increase. Rarely venous wall calcification is prominent.

Primary or simple varicosities often develop in the second and third decades of life and may be present for many years without causing symptoms or complications. The likelihood of thrombosis with propagation into the deep venous system and the development of the postphlebitic syndrome is sufficiently great to warrant their removal. The use of sclerosing agents is contraindicated because of the danger of deep venous thrombosis as well as the temporary nature of the superficial venous occlusion obtained. The operative removal of varicosities is best performed by venous stripping techniques and excisions (Myers).

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LYMPHATICS

ith the exception of certain rare tumors related to lymph vessels such as lymphangioma and lymphangiosarcoma (see Chapter 22, Soft Tissues), the y lymphatic disease encountered clinically is lymphedema. Of course, chylo- and chyloascites occur, but in nearly all instances these processes are sec to trauma neoplastic disease, or some infectious process Lymphedema e classified as postinfectious posttraumatic, obstructive and idiopathic. Ob- ve lymphedema is most commonly seen following the obstruction of regional nodes by neoplastic invasion or following their removal as in radical mastec or in radical groin dissection The development of lymphedema of the fter radical mastectomy is thought more likely to follow in those patients in postoperative infection has produced fibrosis in the axilla or in those having ent cancer in the axilla However lymphedema is seen in patients who give ry of as little trauma as a severely sprained ankle and following such infec as a furuncle Many patients give no history of trauma or infection ted with the onset of their lymphedema In such instances the lymphedema is termed idiopathic or lymphedema praecox. Congenital lymphedema is considered in this category and is differentiated from lymphedema praecox n that the patient has had some degree of swelling of the extremity since) idiopathic lymphedema may develop in persons as late as the age of 40

athology of Lymphedema.—The obstructive nature of neoplastic involve of regional lymph nodes is obvious. In this condition the swelling is usually progressive There is dilatation of the dermal lymphatics as well as the fascial lymphatics (Fig 972) (Butcher) When the degree of swelling is ced there is depression of hair follicles and gross dermal edema. In such the cutaneous lymphatics may be sufficiently dilated to be associated with orrhea following minor cutaneous abrasions or needle punctures (Fig 973) sections of such skin usually show markedly dilated dermal lymphatics

ll forms of lymphedema probably are in some way associated with made lymphatic drainage Drinker has postulated that the increased protein con f the lymph present in chronic lymphatic stasis stimulates the deposition ous tissue in the skin subcutaneous tissue and fascia. Such fibrosis aggravates egree of inadequate lymphatic drainage and makes the disease slowly pro- e. Whatever the mechanism be, the slowly progressive nature of lym ma in many patients is associated with dermal thickening and collagenous tion in the subcutaneous tissues and fascia. Bouts of superficial cellulitis and angitis often become superimposed upon the lymphedema in an extremity ne patients recurrent bouts of such infections are completely incapacitating presence of recurrent infection in such an extremity appears to hasten the ition of collagen and may result in such a large amount of fibrotic replace



Fig 972—Photographs showing injection of enlarged cutaneous lymphatics with 4 per cent sky blue dye The patient had obstructive lymphedema in the inguinal region caused by Hodgkin's disease. The initial injection was made on the lateral aspect of the thigh *(A)* Four hours after the injection, extensive retrograde filling of cutaneous lymphatics on the skin of the medial thigh had occurred *(B)* (From Butcher H R., and Hoover A. L.: Ann Surg 142: 633 1955)

ment of subcutaneous fat and normal dermal structures as to make demonstration of dermal lymphatics impossible. Kinmonth has reported the presence of dilated valveless deep lymphatic channels in idiopathic lymphedema. These were visualized at operation after the injection of patent blue dye and by roentgenologic lymphangiography. Although many varicose like lymphatic trunks were found in his patients, in none was a definite proximal site of lymphatic channel obstruction discovered. In a few patients with idiopathic lymphedema having no clinical evi

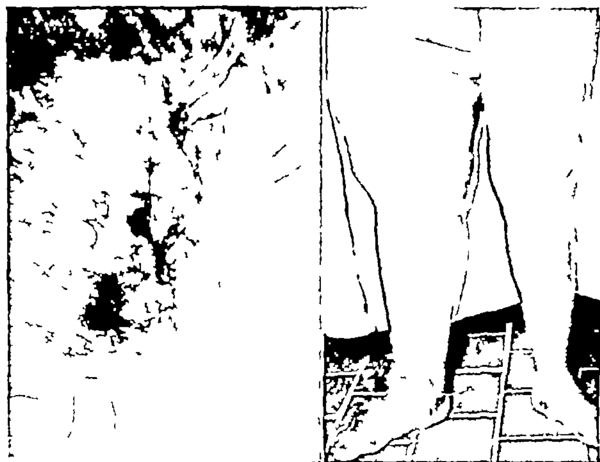


Fig 973.—*A* Photograph of dye-filled skin lymphatics in the leg of a patient with obstructive lymphedema. *B* Following cutaneous puncture for the injection of lymphatics dye-containing lymph flowed from the site. (From Butcher H. R. and Hoover A. L. Ann Surg. 142: 633 1955.)

dence or history of lymphangitis or cellulitis in the extremity, enlarged regional lymph nodes have been removed. Microscopically they contain a mild chronic inflammatory response, sinusoidal fibrosis and markedly dilated lymphatic channels (Fig 974). Despite such findings the pathogenesis responsible for the inadequate lymph drainage in most cases of lymphedema remains unknown.

Treatment of Lymphedema.—Treatment consists primarily of elevation of the extremity compression and massage which must be maintained during many years of supervision. Such conservative measures will control the lymphedema sufficiently to avoid operation in many patients. Operative therapy is indicated only when the extent of subcutaneous fibrosis infection and massive swelling is sufficient to markedly handicap the patient. The operation most useful is the excision

of the thickened fibrotic skin the edematous subcutaneous tissue, and the thickened fascia overlying the muscles followed by the immediate application of split thickness cutaneous autografts (Fig 975) The Sistrunk modification of the Kondoleon operation is no longer considered of value The use of hyaluronidase and long nonabsorbable subcutaneous sutures extending from the lymphedematous areas into the normal subcutaneous tissue have not proved of value (Foley)



Fig 974—Photomicrograph showing markedly dilated lymph channels in an enlarged lymph node removed from the groin of a patient with idiopathic lymphedema of the obstructive type.

In patients with sufficiently severe lymphedema to require excision of the skin subcutaneous tissue and fascia of the extremity gross examination of the excised portions show dense fibrotic bands and sheets extending through the markedly swollen subcutaneous tissue Pockets of fluid may be found in the intervening tissue spaces at operation (Fig 976) The skin over the fibrotic dermis may be atrophic in some areas and hyperplastic and keratotic in others. The collagenous thickening of the dermis is usually extreme Lymphatic channels as such are often not seen histologically in such skin and subcutaneous tissue. This is particularly true if the process has been associated with multiple episodes of dermal infection. Dilated dermal lymphatics may be demonstrated histologically and by dye injection techniques in the skin of a lymphedematous extremity unassociated with long standing episodes of infection (Fig 977)

The dermal and subcutaneous fibrosis similar to that seen in advanced forms of lymphedema also occurs about long standing chronic stasis ulcers. The ob-



Fig 975 —Pre and postoperative photographs of a patient with long-standing infectious lymphedema. All fibrotic skin subcutaneous tissue and fascia were removed and the defect covered with split thickness cutaneous autografts. (W U neg 55 2266) (From Butcher H. R., and Hoover A. L. Ann. Surg 142: 633 1955)



Fig 976 —Photograph of a lymphedematous leg at operation. Arrows indicate large fluid pockets in the subcutaneous tissue. (W U neg 55-3925)

Fig. 977 —Photograph showing unusually dilated superficial cutaneous lymphatics in the skin of a patient with idiopathic lymphedema. (From Butcher H. R. and Hoover A. L. Ann. Surg 142: 633 1955)

literation of dermal lymphatics however, cannot be related primarily to the etiology of stasis ulcers since similar obliteration occurs in the fibrotic skin of long standing lymphedema, a condition rarely associated with chronic ulceration of the lower extremity

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Chapter 25

CENTRAL NERVOUS SYSTEM

DAVID E. SMITH, M.D.

INTRODUCTION

The surgical pathology of the central nervous system has certain characteristic problems that are derived from the unique properties of the organs involved. Clinically the signs and functions of distant somatic regions give rise to a symptomatology that is often apparently far removed from the site of the disease. The rigid confinement of the brain within the skull causes certain common symptoms in many surgical diseases of that organ and also makes it peculiarly susceptible to the effects of violent trauma. Pathologically the unique character of the tissue derived from neuroectoderm gives rise to histologic problems that are different from those of all other tissues. The peculiar physical arrangements of blood vessels and the lack of lymphatics affect the development or occurrence of disease in manners different from those in other organs, while the existence of an entire fluid circulation of its own is the foundation of other unique phenomena.

Techniques

For practical purposes the technical procedures necessary for the histologic diagnosis of neurosurgical diseases are essentially the same as those employed for diseases of other organs. The great battery of special stains formerly employed in medical neuropathology needs rarely be invoked today. Even the metallic impregnation techniques (particularly those of del Rio Hortega which were so effectively applied by Bailey and Cushing and others in the early informative studies of tumors of the brain) are not so necessary now that the various tumors have been so well defined with more practical stains. Only rarely and then more for the satisfaction of the investigator's curiosity than to obtain useful prognostic information need resort be made to such techniques. Basic reliance can be placed upon a routine stain such as the hematoxylin and eosin augmented as necessary by a good silver impregnation technique for reticulin such as Wilder's and by Mallory's phos

photungstic acid hematoxylin stain The latter is particularly useful for the sharp manner in which it separates collagenous tissue from glial tissue and demonstrates the fine glial fibers of astrocytes.

The use of frozen sections in neurosurgical diagnosis is governed by the same principles which apply in other operations The very soft consistency of brain tissue necessitates considerable skill in preparing good sections and preliminary fixation with hot formalin is of aid. Various stains may be used, but thionine is quite satisfactory The principal problem in the diagnosis by frozen sections consists of the distinction between glial tumors and other tumors such as meningiomas, and reactive gliosis. The apparent cellularity of the thicker frozen sections can sometimes be confusing to the inexperienced observer Careful attention to the cytology and histology of frozen sections however allows considerable adequacy in histologic diagnosis by the use of this technique.

General Considerations and Symptomatology

The diagnostic problems that usually confront the neurosurgeon can be divided into five principal topics congenital defects vascular diseases, traumatic lesions inflammatory diseases, and neoplasms. To these may be added the study and diagnosis of intrinsic diseases of muscles and peripheral nerves

In the clinical consideration of each of these categories the problems of the symptoms and effects of increased intracranial pressure are often dominant. This has led to a customary division of the symptoms and signs of neurosurgical diseases into two groups the general and the specific or focal. These are more properly discussed at greater length in special works on neurologic diagnosis but are due basically (1) to the inflexible confinement of the central nervous system within the skull and vertebrae so that any addition of tissue or fluid must be compensated by compression or removal of a pre-existing structure and (2) to the functional disturbances or deficits in sensation or motor activity that result from destruction of areas of specific representation within the nervous system The most common general signs are headache, *papilledema*, vomiting giddiness, convulsions, *abducens* palsy disturbances of mentation, and less commonly bradycardia and respiratory dysrhythmias. The roentgenogram supplies certain other signs of increased intracranial pressure or space-occupying lesions such as the evidences of atrophy about the sella turcica and on the inner table of the skull and detectable shift in the position of a calcified pineal body Examples of specific or focal signs are the uncinate fits that accompany involvement of the temporal lobe in the neighborhood of the hippocampus, field defects resulting from interruption of the optic tracts or projection fields, recognizable disturbance of cerebellar functions from involvement *of that organ and, less frequently recognizable deficit in extrapyramidal ac*tivity characteristic of the corpus striatum, or sensory disturbance of a nature that can be recognized as thalamic in origin. Lesions in the brain stem and spinal cord can often be almost pinpointed by careful consideration of the disturbances of particular functions known to be associated with tracts or nuclei that are of constant location. None of these signs, either general or focal, gives any but inferential evidence however of the nature of the underlying lesion.

Effects of Increased Intracranial Pressure

In addition to the diagnostic import of the phenomenon underlying the signs and symptoms of increased intracranial pressure certain pathologic conditions are created by this pressure and account for important complications that constantly lurk as unpleasant possibilities in the background of most neurosurgical cases Principal among these are the herniations that occur at the foramen magnum and through the incisura tentorii These are most likely to accompany supratentorial space taking lesions The compression of the medulla as a consequence of its being wedged between the cerebellar tonsils and the rim of the foramen magnum

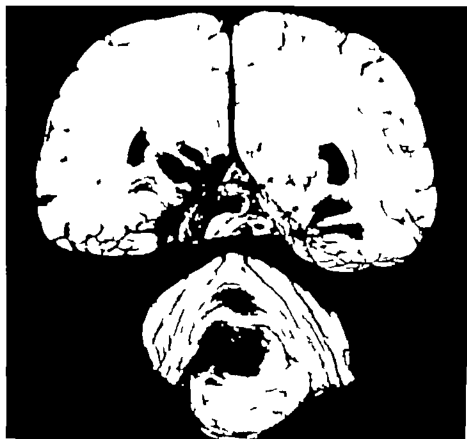


Fig 978.—Bilateral hemorrhagic infarcts in the distribution of the posterior cerebral arteries and venous hemorrhages in the tegmentum of the pons that resulted from incisural and foramen magnum herniations in an untreated case of astrocytoma of the frontal lobe (W U neg 50-1272.)

has been blamed for death due to respiratory or cardiac arrest and accounts for the general reluctance of neurosurgeons to consent to diagnostic lumbar punctures in patients suspected of space-occupying cerebral lesions The removal of more than a drop or so of cerebrospinal fluid by such a procedure is considered particularly dangerous. Such events are fortunately rare, and careful examinations of the entire medical histories of a very high percentage of patients with brain tumors will reveal that a lumbar puncture was performed at some time after the onset of symptoms and before operation with no appreciable untoward effects.

Hemorrhages into the mesencephalon and pons are more commonly proved complications of increased intracranial pressure with herniations at the incisura and

foramen magnum. Poppen observed an incidence of 14 per cent in 258 fatal cases of supratentorial lesions. The lesions are particularly prone to occur shortly after operations but may occur spontaneously. It is impossible to estimate how often they may develop without a fatal outcome, but their occurrence in patients who survive is occasionally suggested by the signs of increased disturbance of oculomotor and pyramidal tract function with depression of consciousness or coma. The demonstration of old hemorrhages in these sites at autopsy, however, is very uncommon. The pathogenesis of this lesion is dependent upon the fact that the venous drainage of the brain stem flows almost entirely upward to join the vein of Rosenthal and finally the vein of Galen, or downward into the spinal venous plexus. The herniation of tissue into the incisura tentorii and the foramen magnum compresses these paths of venous outflow and is followed by congestion and rupture of vessels in the venous bed. These hemorrhages are nearly always venous or capillary in origin, as evidenced by their infiltrative nature, rather than arterial, which have a destructive and dissecting character.

Infarction of the medial and inferior temporal and occipital cortices also occurs as a complication of transtentorial herniation. In this event the posterior cerebral arteries are compressed in their course around the mesencephalon, and the resulting lesions are usually symmetrical hemorrhagic infarcts on the medial and inferior surfaces of the occipital and posterior temporal and parietal lobes. The lesions obviously involve the visual cortex, but the comatose condition of the patient generally prevents recognition of the resulting defects.

CONGENITAL DEFECTS

Congenital defects of the central nervous system that are amenable to surgical correction are usually associated with defects in the development of its bony coverings. Less commonly, defects in the pathways of the flow of cerebrospinal fluid can be corrected.

Spina Bifida: Meningoceles, Encephaloceles, and Meningomyeloceles

The group called spina bifida are the most common of such congenital defects. They are basically failures in the proper midline closure of tissues over the neural tube and as such are but one manifestation in a series of malformations ranging from a completely open neural tube as in craniorachischisis to the imperceptible lesions of occult spina bifida. A true meningocele is a sac composed only of meninges, but only rarely is the underlying nervous system completely normal. If portions of the nervous system are included in the sac, the lesions are called meningomyeloceles or meningoencephaloceles as is appropriate. Meningomyeloceles are about three times as common as simple meningoceles and are more serious lesions because the greater abnormality of the nervous tissue is responsible for greater neurologic deficit.

The predominant site of these defects is in the lumbar and sacral regions of the spine. Fisher observed over 70 per cent of 536 lesions to be in this region. The second most common site is the cervical or occipitocervical region, while occasional examples are found at all points along the cerebrospinal axis from intranasal to

intrapelvic positions. Fisher reported the rather common association of these lesions with other congenital defects, particularly hydrocephalus in over one fourth of the cases. The hydrocephalus is usually due to the Arnold-Chiari malformation which Russell states was present in all cases of meningomyelocele that she has examined Motor disability and sensory disturbance are the most common defects that result from these lesions, some degree of the former being detectable in 91 per cent of the cases Involvement of the urinary and anal sphincters occurs in about two thirds and one half of the cases, respectively and is responsible for the most serious threat to the patient's life other than the accidental rupture or erosion of the sac with consequent meningitis

The sac of a meningocele is composed of a more or less complete outer layer of skin over an irregular layer of dense collagenous tissue mixed with various amounts of fat and representing tissue derived probably from the dermis subcutaneous tissue and dura mater The inner lining is a thin smooth layer of flattened cells. In the more common meningomyeloceles and encephaloceles varying types and amounts of nervous tissue are found in or attached to the walls Normally developed myelinated nerves or nerve roots are most commonly found, but pieces of choroid plexus or islands of isolated neuroglial tissue are often present. The latter can be discovered at considerable distances from the main cavity or mass of central nervous tissue

If the lesions are not too large operative repair may be successful in obliterating the sac. The progression of hydrocephalus when present may be halted but neurologic deficit is never improved In cases where neither hydrocephalus nor neurologic disability is present Fisher reports that they rarely appear after operation Operative mortality and postoperative deficit are much greater in cases of spinal lesions than in those of cranial lesions the majority of patients with the latter lesions being normal after operation.

Teratoid Tumors

Nasal Glioma and Sacrococcygeal Teratoma.—Nasal gliomas and many lesions that have been called sacrococcygeal teratomas are congenital tumors that are apparently closely related to encephaloceles or myeloceles. The nasal gliomas are solid masses of glial tissue, rarely including neurons, that lie in the subcutaneous tissues at the root of the nose or beneath the mucosa of the upper nasal cavity They may be connected by fibrous bands to the components of the central nervous system, but in contradistinction to encephaloceles they contain no fluid filled spaces in communication with the subarachnoid space. They are rare but interesting lesions, for they seem to represent a bridge between pure anatomic deformity on one hand and low grade neoplasia on the other Most of these lesions are present at birth and enlarge only proportionately to the growth of the child A few, however have shown an ability to enlarge more rapidly, and others have recurred as sizable masses after apparently complete removal (Black) True teratomas with tissue typical of derivation from all germ layers also occur in these sites.

Nasal Neuroblastoma.—This tumor usually has the typical histologic characteristics of a neuroblastoma The cells are small and round, are arranged in com

partments partially outlined by a fine fibrovascular stroma and have round dense nuclei and scanty cytoplasms. This tumor is thought to arise from the ganglion cells of the olfactory placode Most cases are discovered as intranasal tumors in young adults and McCormack states they may be as frequent as to be 3 per cent of intranasal tumors exclusive of polyps. It is reported that their histologic patterns vary from those with an epithelial appearance that have been called neuroepitheliomas to others with a prominent fibrillary stroma of cell processes as can be seen in neuroblastomas of other sites such as the mediastinum. Prognosis might be related to these immature or mature patterns but experience has hardly been sufficient to justify confidence in such predictions Some of these tumors have been observed to metastasize distantly and several have apparently been cured by local resection with or without radiation. The tumor would be expected to be sensitive to x radiation but is reported to have been resistant in several cases.

Retinal Anlage Tumor—Peculiar pigmented tumors of the maxilla, mandible, and even of the cranium have been interpreted as having their origin in displaced portions of the embryonic anlage of the retina. These tumors have all occurred in infants. They are composed of cells with the general appearance of neuroblasts, often with abundant fibrillary cytoplasms or stroma, and cells of epithelial appearance that contain prominent granules of melanin and line clefts. These tumors have behaved benignly as far as the reported cases have been followed although one case showed histologic evidence of intravascular growth. Lucas has identified tumors previously reported as congenital melanoma of the face pigmented ameloblastoma and melanotic epithelial odontoma as belonging to this group One case of a similar pigmented tumor in the epididymis is thought to have arisen from a teratoma, but all other recognized instances have occurred at sites to which it seems possible a portion of the retinal anlage, which is originally derived from neuroectoderm could have been physically displaced.

Pilonidal Sinus.—The pilonidal sinus at the tip of the coccyx is another lesion whose pathogenesis may be related to incomplete development of the tissues about the nervous system. In their simplest form they are tracts lined by epidermis that extend beneath the skin toward the dura presumably at the site of the embryonic posterior neuropore. They characteristically give symptoms for the first time in early adult life coincident with the development of increased growth of hair and activity of sebaceous glands that occurs at puberty Trauma often plays a part in the precipitation of symptoms, for the lesion is clinically silent until the hair, desquamated cells, and bacteria in the lumen of the sinus rupture through the epithelial lining and establish a foreign body reaction with greater or lesser degrees of infection and acute inflammation. The more complicated forms of these lesions extend to or through the dura and are attended by the possibilities of epidural abscesses and even meningitis.

It seems clear that not all pilonidal sinuses are due to congenital defects. Some contain little or no trace of an epithelial lining There is a similar lesion that occurs in the interdigital webs of the hands of barbers and is due to fragments of hair working their way through the skin to cause inflammation foreign body reaction and sinus formation. Hall has reported the rare occurrence of epidermoid carcinoma arising in a pilonidal sinus

Dermoid Sinuses and Choristomas.—Other lesions closely related to congenital pilonidal sinuses occur in the lumbar and sacral region, or occasionally higher. These dermal sinuses consist of midline tracts lined by epidermis, with or without skin appendages, that extend through a spina bifida and the dura to a terminal mass of tissue that is often attached to the filum terminale or the abnormally low end of the spinal cord. They may be multiple. The terminal intradural mass of tissue is interesting because it varies greatly in different cases and is another example of the strange connection of congenital deformities and low-grade neoplasia in the central nervous system. Some lesions are composed purely of the fibroadipose tissue that surrounds the descending tract and have been called lipomas or fibrolipomas. Others are terminal expansions of the epithelium-lined tract and have been called epidermoid or dermoid cysts depending upon the presence of skin appendages. Still others have a sufficient mixture of striated muscle, glands, and abnormal nervous structures, in addition to squamous epithelium and fibroadipose tissue to justify the appellation teratoma. They, like pilonidal sinuses, may give difficulty by allowing contamination of the subarachnoid space with resultant meningitis. The gradual enlargement of the tumor may also cause pressure upon nerve roots or the spinal cord with consequent loss of function. The lesions apparently grow very slowly, even when composed of a teratoid mixture of tissues, and malignant transformation is apparently rare. Lesions detected in infancy are usually accompanied by a sinus or at least a dimple in the midline of the back; occasionally there is an apparently similar lesion without communication to the surface that appears as a spinal tumor in an adult. A range of examples with or without associated spina bifida and caudal displacement of the spinal cord suggests relationships between these dermal sinuses and lesions that are choristomas of the meninges. The commonest of these latter are the epidermoid inclusion cysts, but lipomas of the central nervous system belong in the same category.

Epidermoid Inclusion Cysts.—Epidermoid inclusion cysts of the central nervous system are usually classified as tumors, yet they are not neoplasms. These are rare lesions that comprise less than 1 per cent of all central nervous system tumors. The transition examples mentioned in the preceding paragraph indicate their kinship to congenital deformities, and their usual sites of occurrence confirm the impression. They are found for the most part as tumors in the spinal cord, in the suprasellar region (where they are a variety of the craniopharyngioma and have a similar embryonic basis), in the pineal region (which in the early embryo is at the apex of the cephalic flexure and consequently in a position immediately beneath the ectoderm), and at various positions over the convexities of the cerebral hemispheres (where they are associated with defects in the diploë so that the mass may be predominately beneath the dura, or within the skull or beneath the scalp with perplexing unpredictability). Other examples are found in the cerebellopontine angle or petrous portion of the temporal bone where their embryologic origins are less clear but are probably associated with the formation of the pharynx, middle ear, and base of the skull. These lesions should not be confused with the so-called cholesteatomas of the middle ear which are associated with chronic inflammation and may erode through the temporal bone to extradural positions.

The lesions of the central nervous system are more or less clearly within the leptomeninges and are not isolated within the brain substance. Like similar lesions in other organs, they have a central mass of desquamated squamous cells, the in descence of which has resulted in the names of pearly tumors and cholesteatomas. About this central mass there is a layer of squamous epithelium that is essentially epidermis and then a layer of fibrous tissue continuous usually with the leptomeninges and equivalent to the corium. In some tumors skin appendages such as sweat or sebaceous glands and hair follicles are present in this outer layer so that the terminologies of dermoid cyst in contradistinction to epidermoid cyst have been applied. No detectable differences in the biology of the two groups are apparent. Depending upon whether there has been an escape of the contents of the cyst, the surrounding fibrous tissue may contain evidence of a foreign body reaction and chronic inflammation The adjacent brain substance shows only the effects of pressure which may lead to a loss of neurons with diffuse hypertrophy and hyperplasia of astrocytes.

The symptomatology of these lesions is that of a very slowly expanding tumor unless there is a rupture whereupon the signs of acute meningeal irritation supervene. Most of the lesions become manifest in early adult life. Apparently the lesion expands at about the same rate as its surrounding encasement until after puberty It then either continues to increase in size, while the other tissues cease to grow or there is accelerated accumulation of the contents of the sac. Sizable lesions sometimes cause such severe displacement and deformity of the structures of the central nervous system as to cause amazement at the degree of anatomic deformity which this delicate organ can tolerate with apparent complete physiologic compensation. The very slow enlargement of the lesion is probably the explanation of such unusual cases.

Hydrocephalus

Hydrocephalus may be secondary to congenital defects of the nervous system or its coverings, or it may follow other lesions such as tumors, inflammations, or hemorrhages. The first type is sometimes misnamed primary hydrocephalus, while the problems of the second group are largely those of the underlying disease. When hydrocephalus is secondary to congenital defects the deformity is apparent at birth or develops soon thereafter It is probably always associated with a block in the pathways of the flow of cerebrospinal fluid, although it is undeniable that such a block is difficult to demonstrate in all cases Hyperactivity of the choroid plexuses might be a contributing factor in some cases such as those of a choroid papilloma. A common site of the block is at the aqueduct of Sylvius, which may be obliterated or narrowed by congenital malformation so that it is a group of small branching channels. It may also be narrowed by a tumor or a vascular malformation in the mesencephalon, or a severe ependymitis may result in obliteration of the canal. The outflow paths of the fourth ventricle the foramina of Luschka and Magendie, are other sites of possible obstruction. The drainage from the cisterna magna may be impaired by adhesions at its margin or by the pressure of the edge of the foramen magnum in cases of the Arnold-Chiari mal

formation The flow and final absorption of fluid can be affected by adhesions or obliteration of the subarachnoid space over the base of the brain or the convexities. Absence or destruction of the arachnoidal villi is a final possibility. Cases are classified as communicating or noncommunicating hydrocephalus depending upon whether or not a communication between the lumbar sac and the lateral ventricles can be demonstrated This classification is of greater aid in eliminating the possibility of obstruction at certain sites (such as in congenital aqueductal stenosis) than it is in establishing the location of the obstruction at any particular site

The pathologic histology of hydrocephalus is usually disappointing and often obscure. Surgical treatment is aimed at the palliative removal of the excess fluid from some point above the block by any of several ingenious routes—catheters from the lateral ventricles into the cervical subarachnoid space, the cervical subcutaneous tissues, the pleural or peritoneal cavities, a ureter or the middle ear In some cases the process spontaneously resolves itself for unknown reasons and it is sometimes surprising how little neurologic or mental deficit may result from really tremendous deformity

Obstructive hydrocephalus is almost entirely internal hydrocephalus i.e. it is characterized by dilated ventricles. Nearly all cases of external hydrocephalus are due to extensive cortical malformation or destruction porencephaly or meningeal lesions such as subdural hematomas or hygromas

Arnold Chiari Deformity and Platybasia

The Arnold Chiari deformity and basilar depression are two lesions that result in malarrangements between the central nervous system and its bony encasement. Surgical revision of the bones at the foramen magnum is often effective in decompressing the brain stem and spinal cord and relieving symptoms that have arisen on that basis. The Arnold-Chiari malformation is primarily one of the hindbrain. The pons, medulla, and cervical cord are elongated and *sometimes* acutely flexed the cerebellar tonsils are deformed and extend as a cuff ventrally and caudally around the medulla. This results in the medulla lying in the *foramen* magnum and in the foramina of Luschka and Magendie lying below the level of the atlanto-occipital articulation. The upper spinal nerve roots consequently take an upward course instead of running directly lateral as is usual. The deformity is usually but not always associated with a lumbar meningomyelocele and caudal fixation of the lower spinal cord. Because the openings of the fourth ventricle are below the foramen magnum, which is wedged full of medulla and cerebellum, *spinal* fluid cannot rise over the cerebral hemispheres to its usual site of maximal absorption, and a communicating hydrocephalus develops. The deformity of basilar depression is primarily of the pars basilaris of the occipital bone with consequent flattening of the angle of decline of the clivus and impingement of the rim of the foramen magnum on the medulla. Various other malformations of the skull have restrictive effects upon the growth and function of the brain. These conditions have been referred to as craniostenosis. The bone or other surrounding tissue removed at surgical revision of these relationships is of course of normal histologic appearance.

Congenital Cortical Disorders

Cortical biopsy is occasionally employed for specific diagnosis, particularly in children. This is usually a fruitless procedure if no tumor is apparent at exploration, for there are few histologic pictures in the central nervous system that are diagnostically characteristic in such small blocks of tissue as might be removed by biopsy. Among the few lesions that might be so diagnosed are two congenital disorders of the cortex: tuberous sclerosis and amaurotic familial idiocy of Tay-Sachs. The first is characterized by focal disorderly arrangement of neurons, including bizarre and double nucleated forms, and dense gliosis with giant astrocytes and calcification. As actual tumors develop in association with these lesions they must be distinguished from astrocytomas which is sometimes impossible on the basis of only a small sample. This disorder is characteristically associated with the so-called sebaceous adenomas of the face. The cortex in Tay-Sachs disease contains specifically altered neurons that are full of a lecithin so that they have a somewhat spongy cytoplasm which is lightly and irregularly sudanophilic. This disease is more easily identified by the characteristic cherry red spot in the macula. Other conditions such as the degeneration of myelin in Schilder's disease or vascular occlusion and the inflammation of encephalitis or early ischemic encephalomalacia are difficult to define specifically in a small biopsy. Occasionally specific inclusion bodies may be recognized in some forms of chronic encephalitis.

VASCULAR DISEASES

Vascular diseases of the central nervous system may be due to anomalies in formation, abnormalities in the structure, intrinsic diseases, or to rupture and occlusion of vessels. The first two causes include the angiomas and those aneurysms which can be approached surgically. The last two are of interest to the surgical pathologist principally for purposes of differential diagnosis.

Vascular Anomalies

Vascular anomalies are tangled masses of irregular vessels with atypical walls. They undoubtedly have a congenital basis and increase slowly in size so that they are often classified as tumors although there is little evidence that they are neoplasms. They comprise less than 2 per cent of intracranial space-occupying lesions. Anatomically the lesions range from isolated or rather broadly distributed dilated capillary vessels to masses several centimeters in diameter composed of vessels filled with venous or arterial blood. The telangiectases, or capillary hemangiomas, are usually silent lesions discovered incidentally although they may be multiple and associated with the systemic phenomena of Osler's familial telangiectasia. The most common sites are in the pons and mesencephalon near the aqueduct, in the occipital lobes in the white matter about the ventricles, and in the temporal lobes near the temporal horns of the ventricles.

Angiomas.—The more important anomalies of larger vessels are called venous or arteriovenous angiomas. They are most commonly found in the cerebral hemispheres, usually in relatively superficial positions. These are probably dynamic

lesions that enlarge by the dilatation of pre-existent channels. The nondescript character of their walls is caused by the fibrosis incident to the dilatation and the abnormal pressures within their lumens Symptoms are produced by four mechanisms (1) encroachment of the lesion upon the surrounding cortex (2) interference of the flow of blood in the surrounding brain usually by some rather acute change in the lesion itself such as a thrombosis (3) the opening of an arteriovenous communication within the lesion with consequent acute changes in the intraluminal pressures and often with the development of an audible bruit, or (4) rupture of the abnormal vessels Despite the probable congenital basis of these lesions, symptoms do not develop for years, if at all Usually the onset is in the third or fourth decade of life, and the first sign may be convulsions, the symptoms of space-occupying mass or an apoplexy due to the rupture and bleeding from the vessels. Although only one tenth or less as frequent in occurrence as saccular aneurysms, they are the second most important cause of massive subarachnoid hemorrhage.

The tangled mass of vessels has a much more dramatic appearance in situ than after removal. It is practically impossible to distinguish venous from arterial components after their connections to the circulation have been interrupted. Their gross relationships are characterized by the presence of several large vascular channels that lead into and away from the mass. The most prominent of these are on the meningeal surface but unfortunately there is often at least one vessel that arises from the deep perforating vessels of the brain and enters the mass from the underside. Histologically the vessels have irregular walls with large components of fibrous connective tissue and poorly developed smooth muscle. The fibrous tissue often has a hyaline appearance and there is very poor development of elastic lamellae Between the vessels there are usually islands of glial tissue which contain considerable astrocytic gliosis. Smaller telangiectases may be present, and there may be macrophages filled with hemosiderin or fat, depending upon the amount of previous hemorrhage or destruction of surrounding tissue. Calcification is prominent in some of these lesions either in the walls of the vessels or as isolated spherules in the glial tissue, which are thought to originate in the walls of capillaries. When the angioma is principally in the pia arachnoid the calcification may be in the underlying cortex where it is usually accompanied by ectasia of small vessels This calcification is often sufficient to be radiopaque, so that vascular anomalies are among the most common causes of pathologic intracranial calcification. The roentgenographic angiogram is, of course, an almost specific diagnostic tool for these lesions whether they are calcified or not.

Vascular anomalies in the brain occur in coincidence with related defects in the skin of the scalp and face. The combination of a diffuse capillary hemangioma, or flame nevus of the skin (usually along one of the branches of the trigeminal nerve) and a vascular anomaly in the cerebral hemisphere of the same side gives rise to the Sturge Weber syndrome. The coexistence of these deep and superficial lesions has been interpreted as evidence that the basic defect of vascular development appears in the syncytial capillary plexus of the head of the very early embryo before the development of the brain and skull has divided the vessels into

their ultimate distribution. There are various lesions in this region that probably represent incomplete forms of this defect. Angiomas may be present in the dura or diploë, and the subcutaneous lesion may even be a hygroma.

Hemangioblastomas.—Hemangioblastomas have many characteristics of both a neoplasm and an anomaly of blood vessels. Their frequently multiple sites of origin, their familial incidence in about one tenth of the cases and their occurrence with other anomalies in Lindau's disease suggest a basis of congenital malformation, but the high cellularity and evidence of cellular multiplication suggest the qualities of a neoplasm. The onset of symptoms is in the late fourth decade, and as the lesions are usually located in the cerebellum or spinal cord, the signs are characteristic of involvement of those organs. The hemangioblastoma and the

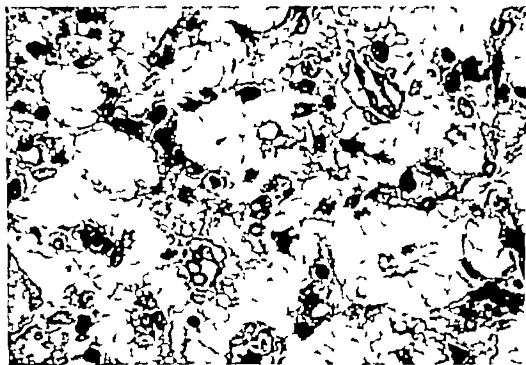


Fig. 979.—Hemangioblastoma of the spinal cord, similar tumors were present in the cerebellum and at other sites along the cord. H and E. stain. (×750.) (W U neg. 49-3707.)

acoustic neurilemoma comprise most of the few primary intracranial tumors that occur in the posterior fossa of adults. Grossly hemangioblastomas are fairly well demarcated lesions usually a deep yellow color due to the amount of lipid in the cells in the stroma. Those tumors with a low content of lipid are pinkish gray unless there has been enough old or recent hemorrhage within them to discolor the tissue. They may be associated with a smoothly lined cyst filled with yellow fluid similar to the cysts of some astrocytomas it has been suggested that the cyst is formed by the coalescence of fluid transuded from the vascular channels of the lesion. In such an event the hemangioblastoma may appear as a mural nodule. Microscopically the lesions are characterized by cords or channels of thick endothelial cells that branch and fade into the stroma of the tumor. The stroma is composed principally of cells that appear to be members of the reticuloendothelial

system the cytoplasms of which may be filled with coarse sudanophilic droplets that usually appear as vacuoles There is some suggestion that the older the patient and possibly therefore, the older the lesion, the higher may be the content of lipid. Occasional mitotic figures are present and when the lesion contains little fat its appearance is quite similar to vascular tumors as they occur in other tissues

Symptoms are apparently precipitated by the gradual increase in size of the mass, possibly by such mechanisms as small hemorrhages transudation of fluid and increase of phagocytosed fat, as well as by cellular proliferation The prognosis of a patient with a single lesion is very good, as spread or recurrence of a well-excised lesion is not to be expected. Even when complete excision is not possible because of the site of the tumor, partial removal may relieve symptoms for a long period. The possible multiple occurrence of these lesions should not be forgotten, however as symptoms from other lesions may develop at a later time. Cramer observed definite evidence of multiple involvement in 5 of 53 cases of hemangioblastoma at the New York Neurological Institute, but because of the absence of clinical symptoms from some of these tumors the incidence is possibly higher than 10 per cent.

The retinal venous angioma described by von Hippel is a characteristic accompaniment of hemangioblastomas but occurred in less than 5 per cent of the cases at the New York Neurological Institute. The lesion of the central nervous system is also found with cysts, vascular anomalies and focal parenchymal hyperplasias in the viscera particularly in the kidneys and pancreas. The rare full blown syndrome of cerebellar, spinal, retinal and visceral lesions is known as Lindau s disease and may occur in incomplete forms.

Saccular Aneurysms

Saccular aneurysms of the cerebral arteries comprise most of the acquired abnormalities of vessels that can be relieved by surgical treatment. They have been called congenital and berry aneurysms but the fact that very few have ever been found in children and none in infants indicates the aneurysms are not present at birth, although certain important factors of formation may be congenital They are the single most common cause of massive subarachnoid hemorrhage and occur most frequently in patients past the fourth decade and in those with hypertension It has even been observed that patients with coarctation of the aorta and consequently hypertension in the carotid and brachial circulations have an apparently increased incidence of saccular aneurysms. Eighty per cent of the lesions occur in that part of the circle of Willis derived from the carotid arteries rostral to the posterior communicating arteries, with a great majority occurring within 3 cm of the terminations of the carotid arteries The middle cerebral artery is most frequently involved followed by the internal carotid and anterior cerebral arteries. Multiple lesions may be found at postmortem examinations in perhaps one fourth of the cases, but it is unusual for more than one lesion to give symptoms. The problem of multiple lesions is important because the refinement of cerebral angiography has made the preoperative localization of these lesions much easier and has occasionally succeeded in demonstrating aneurysms that were not the site of the bleeding or symptoms.

The pathology of the saccular aneurysm is not of diagnostic importance for the lesion is rarely examined before death. Nearly all occur in or very near the acute angles of bifurcations of the cerebral arteries, but when the sac is 1 cm. or more in diameter, it is difficult, if not impossible, to define the site of its opening. This occurrence at the bifurcations has been explained by Forbus as due to the maximum impact of the blood stream at these points plus the presence of folds or defects in the muscle of the media in these sites. Interpretation of the role of these medial defects has caused much controversy and misunderstanding. They



Fig. 980.—Saccular aneurysm of a cerebral artery showing the disruption of the elastic lamella and muscularis at the lip of the mouth of the aneurysm. Lumen of the artery to the left, that of the aneurysmal sac to the right. Verhoeff-van Gieson stain. (×125.) (W.U. neg. 52-4241.)

occur in as many as one third of the bifurcations of sizable cerebral arteries even in newborn infants. It is therefore certain that they are not the sole factor in the formation of aneurysms, and probably they are more important in their localization than in their development. As Forbus points out, the necessary prerequisite for initiation of the aneurysm is probably a defect or weakening of the strongest layer of the wall—the elastic lamella. This would obviously be accelerated by increased intraluminal pressure and would most likely occur at the point of maximum impact especially if that point overlies a discontinuity of the muscular media. Other authors, particularly Dandy, have taken exception to this view and have maintained that most aneurysms occur on the straight parts of vessels at the sites of incomplete absorption of embryonic branches. They support this contention with

the observation that anomalies in the vessels of the circle of Willis in patients with aneurysms are more than usually frequent.

Regardless of the primeval nature of the origins of the aneurysms, the walls of the sacs are composed of fibrous connective tissue and the elastic membrane and muscular media disappear at the edges of the mouth There are usually arteriosclerotic plaques in the wall of the sac or in the vessel about its mouth. Walker suggests that the fortuitous severity of such a plaque may be the initiating factor which accomplishes the destruction of the elastic lamella and weakens the wall of the vessel however the correlation of aneurysms with general arteriosclerosis of the cerebral vessels is poor Factors in the rupture of the lesions are not known other than the suggestion of overdistention of the fibrous sac. After rupture the effects on the surrounding brain vary with the site and direction of the rupture. The bleeding may occur simply into the subarachnoid space, or, if the stream of blood under arterial pressure points toward cerebral substance, the effect may be much like that of a hose playing on sand with extensive dissection and destruction of tissue. Aneurysms of the anterior cerebral arteries sometimes dissect the opposite frontal lobe if the rupture is properly orientated, giving rise to evidence of hemorrhage and enlargement on the side of the normal artery Rupture of the hemorrhage into the ventricles is not uncommon in fatal cases and usually occurs by dissection through the inferior and medial frontal lobe at the anterior extremity of the lateral ventricle

Richardson reported that approximately 50 per cent of patients with ruptured aneurysms recover with no therapy other than bed rest. Repeated hemorrhages occur in 1 out of every 7 patients. Surgical treatment of these lesions attempts to interrupt or decrease the blood flowing into them. This is done by placing clips on the arteries about the aneurysm or by ligation of the carotid artery in the neck. Complications of surgical intervention are usually due to the inadequacy of the cerebral blood flow after occlusion of the arteries at the site of the aneurysm.

Arteriovenous Fistula

Other than the communications between arteries and veins that arise in angiomas, intracranial arteriovenous fistulas develop principally between the internal carotid artery and the cavernous sinus because that is the only intracranial site where there is juxtaposition of a sizable artery and vein. Many are said to be of traumatic origin secondary to basilar skull fractures, but others develop from ruptured aneurysms of the internal carotid artery Symptoms include bruit, pulsating exophthalmus on the affected side, and evidence of disturbances of function of the third, fourth, and sixth nerves Little can be said for the pathology of the lesions other than the gross observation of the communication between the artery and vein, some surrounding fibrous reaction and occasionally sclerotic plaques in the artery fistula, or even the vein.

Cranial Arteritis

Among the intrinsic diseases of the blood vessels of the head cranial or granulomatous giant cell arteritis is most likely to come to the attention of the neuro-

surgeon. It is a febrile, self limited disease of variable duration and unknown etiology The greatest incidence is in women and in the seventh decade of life. Prominent local signs are headache and pain in various structures of the head but systemic symptoms such as malaise, anorexia and weakness may be present. Involvement of the eye with complete or partial loss of vision may occur in as many as one third of the cases. Cerebral symptoms may suggest focal ischemic damage or an encephalitis. A tender nodule is usually palpable along the course of the temporal artery The disease may involve other cranial arteries and has been reported to occur concomitantly with similar lesions in arteries elsewhere, but there is some suggestion that it is related to a rather specific type of senile elastic degeneration and perielastic hyalinosis that occurs in the normal temporal artery

Histologically cranial arteritis is a fibrosis of the intima with focal necrosis and granulomas of the media characterized by the presence of a few giant cells and an infiltrate of round cells but very few or no eosinophils. Kimmelstiel describes the giant cells in association with the disrupted internal elastic membrane and considers the presence of fragments of that tissue in the cytoplasm of the giant cells as pathognomonic of this entity Otherwise the changes are similar to those of polyarteritis nodosa. No specific therapy is known but symptoms are often relieved by taking a biopsy presumably due to the interruption of the periarterial plexus of nerves.

Acute Encephalomalacia

Acute encephalomalacia or ischemic infarction is one of the few other vascular diseases of the brain that comes to the attention of the surgical pathologist inas much as this lesion in its early stages may be accompanied by tremendous edema and swelling of the affected tissue and ventricular displacement suggestive of a tumor The surgeon has no difficulty in recognizing the tissue as abnormal and rarely is there an opportunity to demonstrate the actual causative lesion in the deeply buried blood vessel serving the involved region Although the arterial circulation of the brain is endarterial in pattern there are innumerable communications at the capillary and precapillary levels between the distributions of the various major arteries It is apparently by means of these connections that fluid enters the damaged tissue to cause the remarkable swelling Pathologically this tissue is usually seen only in the acute phase when its gross characteristics are principally its softness and moistness. Microscopically the elements of the tissue are irregularly separated and perivascular and pericellular spaces are widened but empty There may be small foci of diapedesis of erythrocytes. The most frequent definite histologic change is a leukostasis in the capillaries and small vessels with occasional small fibrin thrombi and migration of leukocytes through the vascular walls. Neurons may retain an essentially normal appearance for several days after the onset of symptoms. There is no evidence of proliferative glial reaction. The lack of lymphocytic cellular infiltrate about larger vessels and of the evidence of damage or death of individual neurons distinguishes this picture from that of an encephalitis. Not until three to five days after the onset do macrophages, peripheral vascular proliferation and other better recognized reactions to an infarct appear

By then the edema has largely subsided and there is less chance of the case being presented as a neurosurgical problem.

Pseudotumor Cerebri

This syndrome consists of the rather sudden appearance of the signs of increased intracranial pressure without other signs or symptoms suggestive of etiologic factors. Almost half the cases occur in persons in the third decade of life. The ventricular system on ventriculography is normal and the cerebrospinal fluid is normal to examination and analysis. Zuidema determined by follow up of a large series that there were three etiologic groups into which such cases could be eventually assigned (1) early and otherwise undetectable brain tumors, (2) dural sinus thrombosis that is usually a sequela of upper respiratory infection, and (3) a large idiopathic group in which the prognosis for recovery is very good If the brain is biopsied, the tissue is usually remarkably normal but occasionally it may present the histologic picture of acute encephalomalacia.

TRAUMATIC LESIONS

Patients with acute traumatic lesions of the central nervous system comprise a high percentage of those treated by the neurosurgeon Wounds create difficult and perplexing problems in diagnosis and therapy but supply very little material of pathologic interest. The physics of the distribution of forces about the skull and the physiology of acute cranial and spinal injuries are fields of study in themselves. Acute concussion leaves no recognizable morphologic equivalent. Contusion of the brain results only in physical disruption of its substance and acute hemorrhages. Material from more chronic lesions of traumatic origin, however is more likely to come to the attention of the pathologist. The operative relief of posttraumatic epilepsy and even the recognition of some of the syndromes such as the so-called psychomotor epilepsy in lesions of the insular and temporal cortices are still in a developmental stage.

Dural-Cortical Cicatrix

The dural-cortical cicatrix as the lesion responsible for much posttraumatic epilepsy has been ably investigated and explained by Penfield. A fibrous scar and adhesions develop between the dura mater and other extra arachnoidal fibrous tissue and the brain substance Penetrating wounds of the brain and its coverings are most likely to be responsible for the development of this lesion although it can follow skull fractures hemorrhages or abscesses. It is less commonly a postoperative complication because its development is dependent upon the introduction of extraneous fibrous tissue into the brain wound rather than upon the amount of cerebral substance destroyed or removed. This connective tissue stimulates the proliferation of astrocytes which bind it to the surrounding viable brain. Capillaries grow out from the implant of fibrous tissue into the substance of the central nervous system and anastomose with the normal vascular bed in that site. This supplies a direct union of the external and internal carotid circulations Because

the external carotid circulation is subject to much greater variation in flow due to greater vasomotor activity the amount of blood in this newly formed abnormal bed is subject to considerable variation. This unstable vascular bed inevitably has at least an indirect effect on the blood supply of the surrounding cortex, and it is postulated that its variations are the trigger mechanism for the convulsions.

Surgical therapy of this condition consists of accurate delimitation of the electrically abnormal cortex by means of electrocorticograms and its excision along with the overlying fibrous adhesions. The pathologic specimen is an irregular mixture of fibrous and glial tissue that is usually characterized by distinct astrocytic gliosis. There may be macrophages hemosiderin or other evidences of the process of the acute injury depending upon its nature and the length of time since its occurrence.

Cortical excisions for jacksonian epilepsy are sometimes performed in the absence of cortical meningeal adhesions or scars. Such specimens are usually remarkably normal in appearance but deserve full examination as they occasionally contain evidence of an otherwise silent tumor

Subdural Hematoma

Subdural hematomas are of two varieties occurring most commonly at the two extremes of life infancy and old age. The type seen in infants is the result of intracranial hemorrhage which has usually occurred at the time of birth. The infant's skull is deformed and distorted by the pressure and process of birth. This places a tension and shearing force on certain structures such as the tentorium, vein of Galen and other bridging veins. If a major vessel ruptures, the infant dies during or soon after birth, but if bleeding is slow and slight there may be only the symptoms of lethargy that later deepen into coma. Enlargement of the head may be one of the first noticeable signs. Because of the lack of full myelination in infancy paralytic and motor phenomena that might be expected are often lacking The diagnosis and even the therapy can often be performed by aspiration through the fontanel however fluid tends to reaccumulate in the sacs On exploration a thin gray membrane is found forming a sac in the subdural space. It is filled with blood bloody fluid, or sometimes yellow or clear fluid. The membrane itself may have yellow foci, especially on its inner surface. It is usually loosely adherent to the dura but not the arachnoid.

Microscopically these subdural hematomas are usually thin membranes composed of fibroblasts and relatively few blood vessels. The inner surface is often covered by a rather thick single layer of flattened cells that are probably fibroblasts. In the interstices of the tissue there are relatively few lymphocytes and histiocytes, and occasionally foci of hemosiderin. The appearance is rarely as similar to granulation tissue as is often seen in subdural hematomas in adults. Once the blood has been removed, these membranes are apparently completely resorbed into the dura unless there is a bleeding point or a tear in the arachnoid which allows fluid to return.

Essentially the same lesion sometimes develops in response to cerebrospinal fluid that has escaped into the subdural space where it cannot be resorbed. Such

lesions are called subdural hygromas. Their formation is apparently dependent upon the lack of absorptive abilities on the part of the subdural space The fluid is supplied through the tear in the arachnoid that presumably has something of a valvular action. The membrane about the pocket of fluid is not essential to its formation or retention and may consist of little more than adhesions between the dura and arachnoid.

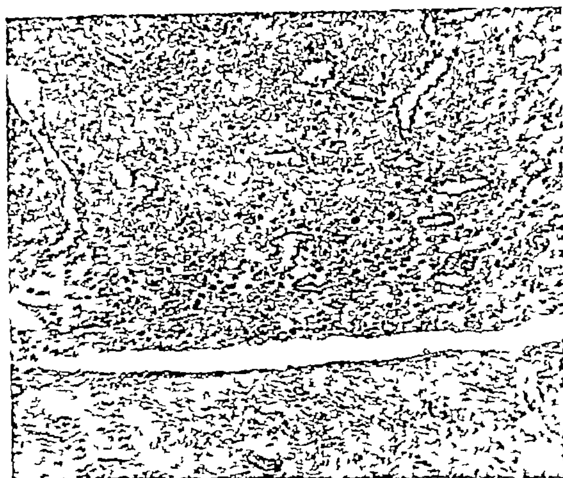


Fig 981 —Subdural hematoma. a cleft demarcates the coarse collagenous tissue of the dura from the overlying organized membrane of the hematoma. Masson trichome stain. (×125) (W U neg 52-4240)

Subdural hematomas in adults are considerably different lesions. Trauma to the head is responsible for their formation in nearly all cases although there may be other factors such as a bleeding tendency or the widened subarachnoid spaces of arteriosclerotic cerebral atrophy that make it possible for this trauma to be so slight as to pass unnoticed. The initial lesion must be a rupture of a small bridging vein in the subdural space, although some authors have suggested that bleeding from arteries or capillaries might also be responsible. This rupture often occurs in the contrecoup position because these veins are stretched by the displacement of the skull in the line of the blow and at the same time are subjected to the convergence of the transmitted forces that pass around the vault of the skull The initial blow may cause a period of unconsciousness due to concussion or even contusion of the brain. In the latter instance the patient's course is usually stormy

from the very start, but it is also just as characteristic for the patient to recover consciousness and be essentially free of symptoms for a period of several weeks. There then appear often rather suddenly the signs and symptoms of increased intracranial pressure which may be accompanied by motor and paralytic phenomena, as these lesions are often near the motor cortex.

Pathologically the well-developed lesion is a discoid sac filled with dark, partially laked blood The gray membrane of the sac may be several millimeters thick. It is grossly similar on all sides of the hemorrhage but is attached to the dura on the outer side. It is smooth and unattached to the arachnoid on the inner side. Microscopically this membrane is composed of large fibroblasts, capillaries with thick endothelial walls, newly formed vessels and endothelial buds, and an infiltrate of histiocytes and lymphocytes. Many of the histiocytes contain hemosiderin, and hematoidin may be present to supply a grossly visible golden color The histologic picture is quite similar to that of granulation tissue except for the absence of prominent numbers of granular leukocytes.

The mechanisms of the development of the complete symptom producing lesion have been well investigated. Leary showed that there were four recognizable anatomic stages which could supply a basis for an estimate of the time from the onset of hemorrhage. For the first eighteen hours the subdural blood remained fluid or formed soft, nonadherent clots. During the second and third days the clots were recognizably firmer and adherent to the dura. From then through the second week the blood was very dark, clotted, and sometimes separated from a yellow fluid. Evidence of organization was visible on the dural surface, but there was no inner covering or neomembrane. The fourth stage consisted of formation of the neomembrane, which was observed in one of his cases to be completely formed thirty nine days after injury After the complete double membrane is formed, it may persist for months or even years with no reliable anatomic changes to represent its age. With completion of the enclosing membrane the hemorrhage becomes a volume of fluid that contains cells proteins, and salts. Zollinger *demonstrated that the surrounding sac had the properties of a semipermeable* membrane when removed intact and connected to an osmometer Furthermore, the protein content of the fluid in old subdural hematomas is a third or less than that of whole blood due to disintegration of the proteins and imbibition of fluid by means of osmotic forces. The source of this new fluid is probably the plasma of the capillaries in the surrounding membrane and its method of accumulation accounts for the late onset of symptoms. The hemorrhage does not have a space occupying effect until the sac is closed and its volume increased However there are also other phenomena that may help explain the clinical course. Hemorrhages of various ages recognizable by the stage of preservation of erythrocytes are often *seen within the membrane so some of the increase of volume (particularly in* hematomas that have been evacuated) may be due to fresh hemorrhages from the thin capillaries in the membrane. There is also a controversy as to the role of intradural hemorrhage in the formation of this lesion, but, to say the least, that theory has not gained general acceptance and would apparently apply more often to the lesions found in cases of vascular disease or hemorrhagic dyscrasias than in those of trauma.

Therapy consists of evacuation of the hemorrhage and removal of the membrane if possible, to prevent its refilling The success of treatment apparently depends more upon the condition of the underlying brain than upon the operative procedure itself As many persons with these lesions are elderly, their brains are atrophied by the effects of arteriosclerosis and arteriolosclerosis With removal of the hematoma the displaced and compressed cerebral tissue does not expand and *return to its normal position, and functional improvement is equally unsatisfactory* Histologic examination of the underlying cortex will principally show thickening of the small vessels and loss of neurons with a slight hypertrophy and hyperplasia of astrocytes.

Chronic Arachnoiditis and Arachnoidal Cysts

Chronic arachnoiditis may follow the introduction of foreign substance into the subarachnoid space This is most likely to occur in the region of the lumbar sac and to be characterized by involvement of the spinal roots of the cauda equina but occasionally a similar etiology is blamed for the formation of pockets of fluid in the subarachnoid space that are called arachnoidal cysts. Recently there has been considerable discussion of this lesion as a sequela of accidents during spinal anesthesia. Its incidence is undetermined, but its crippling effects may be as severe as a paraplegia. The pathologic findings are usually more obvious in situ than they are in a histologic section A distinct thickness grayness and opacity of the membrane can be observed at operation. Microscopically the most that can usually be seen is a bland fibrous membrane that is several times thicker than the normal pia arachnoid but which contains no evidence of inflammation beyond a few lymphocytes. Only very rarely are foreign substances macrophages, and giant cells of a foreign body reaction identifiable.

Not all arachnoidal cysts are clearly of this origin. Some are undoubtedly congenital but all are characterized by the nonspecific histologic character of their walls There are also other rare cystic lesions such as epidural cerebrospinal cysts that are due to herniation of a sac of pia arachnoid through a congenital or acquired defect of the dura. These can occur in the spinal vertebral canal and give the signs and symptoms of cord compression like a tumor Cysts also occur at the intervertebral foramina, particularly of the sacrum where they may compress the spinal nerves. These are often filled with a rather glairy fluid and are thought to be isolated diverticula of pia arachnoid

Ruptured Intervertebral Disc

Ruptured intervertebral discs are lesions of possibly traumatic origin and are of importance principally for the effects they produce on the central nervous system. The great majority of these lesions occur between the lumbar vertebrae and produce signs of irritation and destruction of fibers in the roots of the cauda equina. They also occur at higher sites where they cause pressure upon the spinal cord itself In these instances the root pain characteristic of the lower lesions is not prominent, and instead there result confusing syndromes suggestive of such degenerative diseases as amyotrophic lateral sclerosis. The material removed at operation is only fibroelastic cartilage which may show slight degenerative changes

such as fibrillary stroma and focal calcification The essential pathologic changes are probably in the outer layers of the intervertebral disc which are weakened and destroyed and allow the central portions to herniate. As such they are not observed or available for study

INFLAMMATORY DISEASES

Inflammatory diseases of the central nervous system that are subject to surgical treatment are of two types. In one the process is focal and behaves as a space-occupying lesion (abscesses and granulomas) In the second inflammatory changes in the meninges create the necessity of decompressing the underlying nervous tissue or of relieving the obstruction in the flow of cerebrospinal fluid (hydrocephalus following meningitis and an obscure condition that can be termed a chronic pachymeningitis)

Brain Abscess

Experience with abscesses of the brain has changed greatly in the years since the introduction of modern chemotherapeutic agents Along with acute and chronic mastoiditis which anteceded a majority of brain abscesses the lesion has declined in incidence and its therapy has increased in efficiency No comprehensive studies of the present character of the disease have been published, so most of what is known is derived from earlier experience and modified by personal impressions

It is a lesion of patients in their second to fifth decades. The symptoms are essentially those of an acute intracranial tumefaction Fever is not sufficiently constant to be a reliable symptom. It is often remarked that bradycardia is more common than with tumors presumably because of the more acute development of elevated intracranial pressure. Two thirds or more of the cases were formerly associated with local suppurative disease in the adjacent ear or nasal sinuses a quarter were associated with suppurative pulmonary disease or bacterial endocarditis and the remainder followed trauma or incidental conditions or were of idiopathic origin. These three groupings also indicate the principal methods by which the infection reaches the brain (1) by contiguous spread, utilizing infected thrombi in veins (2) by emboli in the arterial blood stream or possibly distant venous embolization by way of the vertebral veins and (3) by direct inoculation or unknown methods.

The abscesses of the first group were associated with infection of the mastoid from four to nine times as frequently as with infection of other sources such as the frontal or sphenoid sinuses. To a certain extent it is characteristic for lesions of the frontal lobe or anterior fossa to be associated with frontal sinusitis and subsequent osteomyelitis. Those of the middle fossa follow chronic middle ear infection. The cerebellar or posterior fossa abscesses are associated with infected thrombosis of the lateral sinus or chronic labyrinthitis which in turn follows infection of the middle ear or mastoid The abscess is not always immediately adjacent to the focus of chronic infection, however as the inoculum can apparently

carried as an infected embolus in cerebral or diploic veins for considerable stances. In general the proportion of temporal lobe involvement to that of the rebellum in cases following ear disease is approximately two to one

The initial focus of involvement in an abscess is apparently immediately be ath the cortex which with its high content of astrocytes retains the developing sion and prevents its outward rupture although extention forward and into the ntricles is not so opposed Judging by our knowledge of the development of scesses elsewhere there must be an early stage of diffuse pyogenic inflammation llowed by liquefaction of tissue and then formation of a pyogenic membrane. the brain this membrane is much like that of abscesses in other tissues. There an inner zone of necrotic tissue and fibrin heavily infiltrated with leukocytes and middle zone of proliferated capillaries and fibroblasts which respond unusually tensively for lesions of the central nervous tissue. These zones are infiltrated th leukocytes and histiocytes which phagocytize the lipids of the destroyed brain. yond this there is a zone of astrocytic glial proliferation that is naturally charac ristic of abscesses in this tissue A plane of cleavage often exists in this region that well-encapsulated abscesses can be enucleated with removal of very little lherent surrounding brain The pyogenic membrane about an abscess of the ain requires at least two weeks for complete development but its first traces in ounds can be seen grossly in as little as four or five days.

The bacterial etiology of brain abscesses usually involves a staphylococcus reptococcus or pneumococcus Anaerobic streptococci or other anaerobic or nisms are often characteristic of those abscesses associated with suppurative ılmonary disease These latter organisms are difficult to control and probably count for the unfavorable prognosis in this class of abscess

Many different methods of surgical treatment of abscesses have been used. he single most important contribution to their effective therapy has been the odern antibiotics It has been long recognized that operation upon a well ncapsulated lesion gives the most favorable result, but many patients become esperately ill before complete encapsulation takes place. Mortality rates of reater than 40 per cent have been the rule before the spread of infection could e so well controlled by drugs It is significant that in one series of cerebellar scesses only 2 of 9 patients survived before the advent of penicillin while 8 of survived when that drug was used. Chemotherapy is apparently not the whole nswer however and there remains the necessity of surgical drainage or removal f loculated suppuration.

ranulomas Tuberculomas, Gummas, Fungi, and Parasites

Granulomas of the central nervous system are most frequently due to tuber ulosis but may be caused by syphilis or various fungus diseases, such as crypto-occosis, actinomycosis or mucormycosis. Because of their space-occupying prop-rties these lesions present a clinical picture essentially that of a tumor They ake up 2 to 3 per cent of a group of lesions diagnosed at first as tumors. The nfectious inoculum of these lesions is borne by the blood to the central nervous ystem, and its localization there is consequently dependent upon the relative size

and vascularity of the various areas. Being a disease of adults granulomas are, therefore, more commonly found in the posterior fossa than are primary glial tumors.

The histology of these lesions is comparable to that of the same diseases as they occur elsewhere with perhaps a relatively less prominent fibroblastic component in their composition. Fungus lesions vary from those that are more properly described as abscesses to others than are quite solid and like tuberculomas or gummas The specific diagnosis rests upon the recognition of the causative organisms in the tissue or their demonstration by culture.

Parasitic infestations of the central nervous system in cysticercosis or by such organisms as echinococcus are rare in this country Depending upon the number and size of the lesions, they can present the symptoms of either space-occupying masses or a more diffuse process suggestive of an encephalitis.

Chronic Pachymeningitis

Chronic pachymeningitis has been customarily ascribed to syphilis. The typical lesion is said to be a gummatous inflammation of the dura mater in the cervical region that forms a collar about and compresses the spinal cord. There are, however other cases in which there is great thickening of the dura in relatively wide expanses of the skull as well as the vertebral canal. The membrane may reach a thickness of 1 cm. and have the consistency of a tendon. The symptomatology varies with the site of maximum involvement and is likely to include signs of pressure on various cranial nerves the brain stem or the spinal cord. Fever is sometimes present.

Grossly the tissue is a tough grayish yellow membrane several millimeters in thickness. Microscopically it is composed of fibroblasts collagenous fibers, and a light infiltrate of lymphocytes plasma cells and a few leukocytes and eosinophils. The cellular infiltrate is often concentrated in perivascular foci and there may be small areas of necrosis. The blood vessels may be thickened and contain a few inflammatory cells in their walls.

The occurrence of fever in this disease and the localization of the lesion in the dura over the base of the skull have suggested that it may be related to chronic infection and inflammation of sinuses or retropharyngeal tissues. There is no evidence of syphilis in most cases The course is apparently mildly progressive, and surgical removal of the thickened membrane can give worth while relief by decompression of involved structures

NEOPLASMS

Introduction

The biologic characteristics of intracranial tumors are modified by the fact that two thirds of them are derived from a tissue that is set apart in early embryogenesis. This tissue is represented only scantily in the other organs of the body Furthermore, certain unique properties of the encasement of their sites, such as the lack of lymphatics, add to the circumstances that cause these tu

mors to behave differently from many other neoplasms Despite such peculiarities however, the well-established concepts of the inherent nature of neoplasia are as applicable to intracranial tumors as to any other, and many principles derived by experience with tumors elsewhere are supported by observations of this group of neoplasms.

There exist as possible tissues for the derivation of tumors within the central nervous system the neurons, the neuroglia, the reticuloendothelial system (as represented by the microglia and certain cells of the vascular sheaths), and a small amount of mesenchymatously derived tissue in connection with the blood vessels. In addition, other possible sources of intracranial tumors include the meningothelial cell of the pia arachnoid and the Schwann cell of the nerve roots the specific cells of the pituitary and the pineal bodies, the cells of certain embryologic rests such as Rathke s pouch and the notochord and the fibrous osseous and related tissues of the encasement. Certain of these tissues, such as the neurons, rarely if ever undergo neoplastic transformation others, such as the cells of the pituitary and the notochordal rest give rise to slowly growing lesions with the biologic characteristics of a benign tumor, while still others, particularly the neuroglia, undergo changes that satisfy most of the usual criteria of malignant neoplasia.

Intracranial and intraspinal tumors comprise from 2 to 10 per cent of all tumors. The relative frequency varies with the age of the patient Tumors of the nervous system combined with those of the hematopoietic system and kidney comprise the major part of all tumors in infants and children. Of intracranial tumors, about half (Grant, 53 per cent, Bailey 42.6 per cent) are of gliogenous origin, about one sixth are meningiomas one eighth are derived from the pituitary or parapituitary structures and the remainder arise from various other sources

The glial tissue of the fully developed nervous system is capable of malignant transformation Zimmerman has shown that most of the histologic types of gliomas may arise in the brains of mice in response to implanted carcinogens although naturally occurring gliomas in these animals are unknown. The most popular terminology for glial tumors employs names borrowed from embryology such as spongioblastoma, astroblastoma, etc. which has fostered the concept that these tumors actually contain persistent embryonic cells It is more consistent however to think of their development in the same manner as tumors of other parts of the body namely, as a process of proliferating cells losing normal differential properties and acquiring neoplastic characteristics In the more malignant tumors the cells have fewer and fewer characteristics of the well-differentiated parent tissue. Furthermore, in the most undifferentiated tumors it becomes impossible to recognize the derivation of the dominant cell so that probably just as with undifferentiated carcinomas of other organs it is to be expected that highly malignant cells from either of the three basic types of glia might become indistinguishable. The development of a highly undifferentiated tumor from an earlier well-differentiated neoplasm has often been observed Other tumors have shown a preponderance of well-differentiated tissue (consistent with a long history of clinical symptoms) with foci of apparently proliferating undifferentiated tumor that were responsible for recent exacerbations of the symptoms

TABLE 45 TERMINOLOGY OF GLIAL TUMORS

Normal cells	Neurons	Astrocytes	Ependyma	Oligodendroglia		?	Microglia
Well-differentiated tumors	Ganglioastrocytoma (Ganglioneuroma)	Astrocytoma (Astrocytoma Grade 1)	Ependymoma (Ependymoma, Grade 1)	Oligodendroglioma	Mixed glioma		
Undifferentiated tumors	Undifferentiated ganglioastrocytoma (Spongioneuroblastoma glioneuroma)	Undifferentiated astrocytoma (Astroblastoma spongioblastoma polare astrocytoma Grades 2 and 3)	Undifferentiated ependymoma (Ependymoblastoma? neuroepithelioma? medulloepithelioma? ependymoma, Grades 2 and 3)	Undifferentiated oligodendroglioma (?) (Oligodendroblastoma?)	Undifferentiated mixed glioma		
Anaplastic tumors			Glioblastoma multiforme (Spongioblastoma multiforme astrocytoma, Grades 3 and 4 ependymoma, Grades 3 and 4 glioblastoma, Grades 3 and 4)			Medulloblastoma	Reticulum-cell sarcoma

Schema of the Histogenesis of Glial Tumors. Approximate synonyms in current usage are indicated in parentheses. Tumors of very rare or controversial existence are indicated with question marks.

The development of gliomas is probably complicated by the response of more than one line of glia to a carcinogenic stimulus to give rise to the components of a single tumor This is often suggested by the histologic study of well differentiated as well as poorly differentiated gliomas and was interestingly confirmed with trans plantable induced tumors in mice where recognizable differentiated astrocytomas and ependymomas were isolated from parts of an undifferentiated tumor by multiple series transplants.

Table 45 represents these concepts as applied to the terminology of the ma jority of glial tumors. The well-differentiated tumors bear names directly de rived from their obvious glial components and synonymous terms are indicated at various positions The division into three principal strata is consistent with the prognosis of glial tumors The upper well-differentiated stratum represents those tumors in which recurrence occurs slowly three or four years after surgical excision or in which some cures are effected, the middle stratum usually carries a prognosis of recurrence within two years, the lower group rarely shows sur vivals of a year The term glioblastoma multiforme has been used for most le sions of this latter group because its connotation is widely understood. There appears to be little gained by attempting to subclassify its members, especially in view of the increasing atypicality of the undifferentiated cells regardless of their source and the recognized possibility that many, if not all of these tumors are of mixed derivation.

It would perhaps seem justifiable to retain certain of the older divisions of nomenclature, for they have come to carry clinical implications that are almost a syndrome. The polar spongioblastoma as the typical pontine tumor in children is an example. Such an argument has little attraction from a histopathologic view, however, and analysis of these concepts often shows them to be erroneous. Only about a quarter of pontine gliomas for instance, present the typical his tologic picture of the polar spongioblastoma the remainder usually being glioblastomas or astrocytomas It is better to recognize that the complexity of the central nervous system is such that certain areas are analogous to individual organs in other systems, and the brain is itself an organ system In the gastrointestinal tract it is well established that epidermoid carcinomas of the lip esophagus and rectum have different features in their natural history It might, therefore, be expected that tumors of similar histologic derivation would present different char acteristics of growth and occurrence in such diverse sites within the central nervous system as the cerebral hemisphere the optic tracts the basal ganglia the pons, and the cerebellum

Glial Tumors

Astrocytoma.—Astrocytomas are the most common of the well-differentiated glial tumors, comprising approximately one quarter of all gliomas. Many series, however record higher percentages because of differences in the criteria of diag nosis of the more malignant forms Actually because the majority of glioblastoma multiformes are derived from astrocytes, probably two thirds of all gliomas origi nate from astrocytes They occur characteristically as tumors of the cerebellum

in children and of the cerebral hemispheres in adults although they may arise at almost any site in the central nervous system. The average age of incidence occurs in patients near the end of the fourth decade, and men are more commonly affected than women.

Astrocytomas are characterized grossly by a homogeneous firm consistency and gray yellow color They may be either solid or cystic tumors, and their borders although indistinct, can be fairly well defined. The cysts are filled with clear yellow fluid which clots on removal. There are two types of cystic tumors.

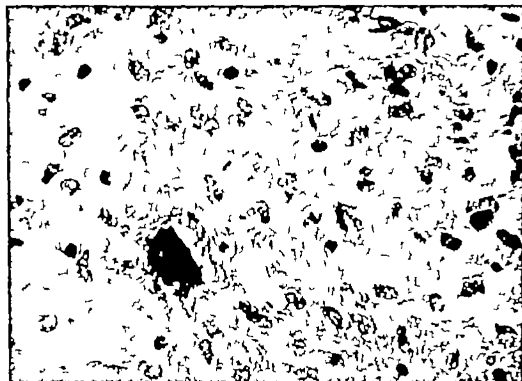


Fig 987—Astrocytoma a well-differentiated slow growing tumor with focal calcification from the cerebellum of a child H and E stain. (×750) (W U neg 52-4235)

One has a central focus of tumor tissue and is surrounded by irregular walls of neoplastic tissue. The other type forms in the glia around a tumor so that the result is a smooth walled cavity with a mural nodule of tumor at one place in its wall. Histologically there are several basic patterns The two basic cellular types are the fibrillary and cytoplasmic astrocytes. The fibrillary astrocyte is a stellate cell with processes that extend in all directions from a scanty amount of cytoplasm about a round nucleus of moderate size and light chromatin structure. The processes of these cells can be outlined by metallic impregnation which gives the cells a spiderlike appearance In routine preparations however and even with the phosphotungstic acid hematoxylin, the processes can be traced for only a short distance from the cell bodies where they become lost in the surrounding mass of fine arborizations of the processes of other cells or pass out of the plane of the section. The cytoplasmic astrocyte has a thick cytoplasm that is deeply stained by eosin and gives the cell an almost spherical outline. The processes are stubby and

irregular The nucleus is usually small rather dense and often eccentric, although it may be more like that of the fibrillary astrocyte.

In addition to the two basic types of astrocytes, these tumors show other histologic patterns that are sometimes classified as separate tumors These include tumors called astroblastomas that contain elongated thick cylindrical cytoplasmic astrocytes which often have prominent perivascular arrangements and attachments Another pattern called the polar spongioblastoma has elongated fusiform fibrillary astrocytes and is often characterized by very coarse glial processes This pattern is most often recognized in certain characteristic sites such as the optic

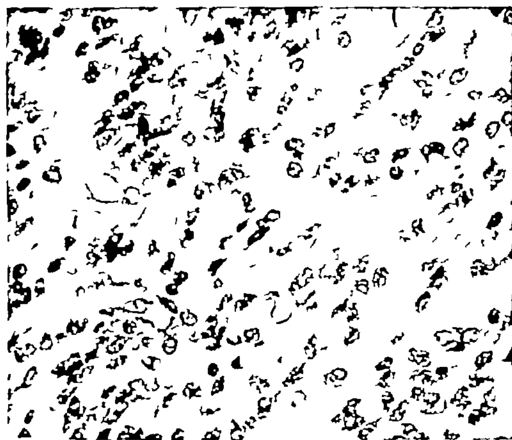


Fig. 983 —Astrocytoma a slightly undifferentiated tumor from the cerebral hemisphere of an adult. H. and E. stain (×750) (W U neg 52-4236)

nerves diencephalon and pons where the tumor cells grow along previously existent fiber tracts which probably give the cells their characteristic elongated shape. Most tumors of these architectural variants show sufficient anaplasia so that many of their cells do not stain in the manner characteristic of normal actively hyperplastic astrocytes a property that has prompted their designation as spongioblastomas or astroblastomas

Astrocytomas can be profitably divided into well-differentiated tumors and other undifferentiated tumors whose histologic and clinical characteristics are indicative of less active growth and malignancy than is characteristic of the glioblastoma multiforme. The well-differentiated type corresponds to what some authors have designated as astrocytoma Grade 1 using a scale of malignancy that

includes the glioblastoma multiforme and ranges from Grades 1 to 4 These well-differentiated astrocytomas are most characteristically found in the cerebellum of children They may involve either the vermis or hemispheres and may be cystic or solid tumors. Histologically they have a broad zone of transition to normal brain. At their centers they have a cellular density only slightly greater than that of normal brain but they destroy the normal architecture of the region involved. The cells are nearly always small fibrillary astrocytes that are apparently growing so slowly that, like normal resting astrocytes their processes are often difficult to stain with phosphotungstic acid hematoxylin There is practically no evidence of pleomorphism of cells no mitotic figures no hyperchromatism or abnormalities of the nucleus, and very little reaction on the part of the vascular stroma. Small spaces filled with a protein-containing fluid, called microcysts, may be present in the interstices of this tumor As many as 15 per cent contain scattered small calcified spherules but these are rarely sufficiently numerous to show in roentgenograms.

This tumor is the most benign of the intracranial gliomas. Two thirds of patients survive more than three years and undoubted cures have been reported. The same histologic type of tumor is much less common in other sites, although when found in the cerebral hemispheres of adults it has almost equally as favorable a prognosis. It is said that the cystic varieties have a more favorable prognosis than the solid, but that is probably because solid astrocytomas seem more likely to contain evidence of anaplasia and to be undifferentiated.

The undifferentiated astrocytoma is distinctly more cellular in most instances than is the better-differentiated type. The transition from normal tissue to tumor is often more distinct, and as many as one fourth of the cells may exhibit pleomorphism of the cytoplasm or nucleus and hyperchromatism Doubly nucleated forms may be present, but multinucleated giant cells are more characteristic of the glioblastoma. Mitotic figures are absent or very rare. There is insignificant necrosis and evidence of vascular proliferation is usually slight. Different tumors of this classification may present distinctly different histologic patterns. Most are mixtures of predominantly fibrillary astrocytes and some irregular and cytoplasmic forms others have bundles of fusiform cells or radial actiniform arrangements called spongioblasts and astroblasts. Nearly all purely cytoplasmic astrocytomas belong to this class. The most characteristic site of these tumors is the cerebral hemisphere, but they are found throughout the central nervous system. This group has a considerably less favorable prognosis than does the well-differentiated astrocytoma. The three-year survival rate is about 15 per cent, and the average postoperative survival is about two years or less before the return of symptoms.

Astrocytomas comprise less than one third of the glial tumors of the spinal cord which in turn are a little less than one fourth of all tumors affecting that part of the central nervous system. Most spinal astrocytomas are well differentiated and so they characteristically present long clinical histories, but because of their intramedullary position operative cure is practically impossible. Glioblastoma multiforme of the spinal cord is rare.

Ependymoma.—Ependymomas are probably more common tumors than are indicated in most published classifications where they usually comprise about 5 per cent of all gliomas This arises from the fact that ependymomas can present strikingly different cellular patterns, and pathologists and surgeons were slow to recognize the interrelationships of this group of tumors They occur in patients of all ages and in all parts of the nervous system Most of these tumors are adjacent to or project into the ventricles but many grow so predominantly into the surrounding white matter that they have very much the same position as any other glioma The average age of occurrence is in the last half of the third decade a little younger than in patients with astrocytoma In children they comprise another component of the characteristic cerebellar tumors while in adults they are usually cerebral or spinal in location

Ependymomas are gray solid homogeneous tumors, usually of a moderately soft consistency There are four more or less distinct histologic types. The most common is the cellular ependymoma which is a solid tumor that grows within the substance of the brain and is composed of uniform cells with oval moderately chromatic nuclei and finely fibrillary cytoplasm. The cytoplasmic boundaries are so indistinct that the nuclei appear to be embedded in a continuous stroma. There is often a pronounced tendency for these nuclei to be arranged in circles or arcs. Around the blood vessels there are zones (50 to 200 microns in breadth) that are free of nuclei and composed entirely of cystoplasmic processes These patterns have been referred to as pseudorosettes Special stains are of no avail in studying these tumors. Metallic impregnation demonstrates no formed processes, phosphotungstic acid hematoxylin stains no glial fibers.

A second type of ependymoma is the epithelial variety in which the cells may be analogous to those of normal ependyma. The nuclei are ovoid and moderately dense without prominence of the nucleolus. The cells may be somewhat columnar and almost epithelial. The cells form tubular and acinous patterns very much like the neural tube, and sometimes blepharoplasts are demonstrable. Some of these tumors with well-developed tubular epithelial patterns have probably been designated as neuroepitheliomas and medulloepitheliomas but a critical study of one of the largest series of cases has demonstrated no biologic justification for the separation of these types.

Myxopapillary ependymomas are a third type. They are rare tumors usually found in the lower spinal cord or filum terminale, but may develop within the cerebral ventricles. The irregular cells have a papillary arrangement with a distinctly epithelial appearance around cores of a loose fibrillary basophilic tissue which contains a substance that stains weakly with mucicarmine. The appearance of these tumors is so striking that they are often not recognized to be of glial origin.

Choroid papilloma may be considered the fourth tumor of ependymal-cell origin They are intraventricular tumors of grossly obvious papillary configuration and may be found in any ventricle. Sizable tumors occur in the lateral ventricles of very young infants. Their intraventricular growth is usually so lacking in symptoms that they reach a very large size and the principal problems in surgery are the approach and the vascularity Microscopically they more or less dupli



Figs. 984-987.—Ependymomas: well-differentiated examples of the four histologic varieties.

Fig. 984.—Cellular type. H. and E. stain. (×280.) (W.U. neg. 52-4258.)
Fig. 985.—Epithelial type. H. and E. stain. (×280.) (W.U. neg. 52-4259.)
Fig. 986.—Myxopapillary type. H. and E. stain. (×280.) (W.U. neg. 52-4260.)
Fig. 987.—Choroid papilloma. H. and E. stain. (×280.) (W.U. neg. 52-4261.)

cate the structure of the choroid plexus with fronds of a vascular stroma covered by cells of almost epithelial appearance. They may invade the brain where they appear as cellular or epithelial ependymomas or they may seed extensively throughout the ventricles

An important fact about the four architectural types of ependymoma is that they have little or no prognostic importance in their own right. The usual features of pleomorphism hyperchromatism, and mitotic figures characterize the more malignant varieties of each group Fortunately, a high percentage of all

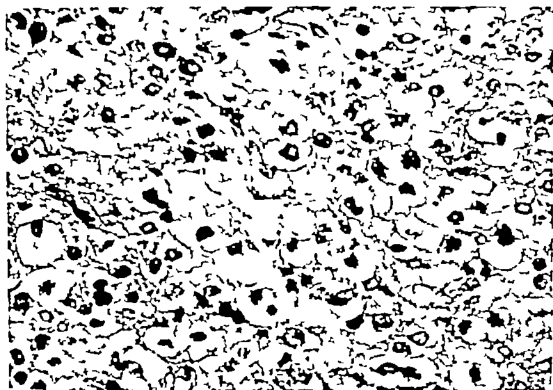


Fig. 988 —Oligodendroglioma with typical perinuclear clear zones of unstained cytoplasm H and E stain. (×750) (W U neg 52-4237)

ependymomas are well differentiated and few possess enough anaplasia and evi dence of rapid growth to be classed with the glioblastomas. At the Mayo Clinic, over 50 per cent of ependyomas were very well differentiated and carried a three year survival rate of almost 80 per cent. These tumors like other slowly growing gliomas, contain calcospherites in about 15 per cent of instances.

Ependymomas comprise over half the gliomas of the spinal cord and about one eighth of all tumors of that organ They are characteristically found more frequently in the lower thoracic and lumbar region because of their tendency to arise in the conus medullaris and filum terminale. Their well-differentiated his tologic pattern particularly in the latter location, and the fact that they exist out side the functional portions of the cord combine to make surgical cures possible and the general prognosis very favorable Systemic metastasis after local in vasive spread has been reported (Weiss)

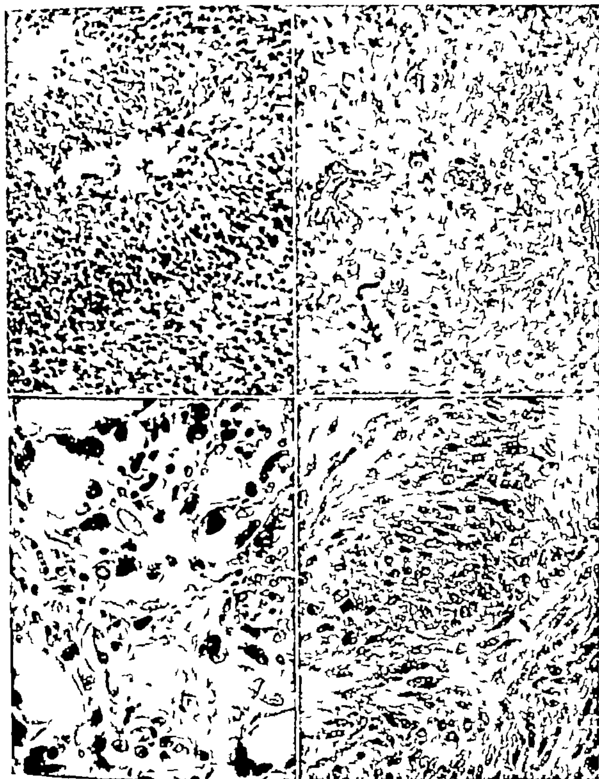
Oligodendroglioma —Oligodendrogliomas comprise the third type of tumor composed of true glial cells They are less common than ependymomas and com

prise less than 5 per cent of gliomas They occur most often in the frontal lobes of adults but have been reported in the spinal cord and cerebellum. The recognizable tumors of this group are very slow growing but as many as a third may arise in a focus in the corpus callosum and spread into both hemispheres Well-differentiated oligodendrogliomas give symptoms for periods as long as forty three months before operation is necessary and although patients survive for an average of four years after operation they ultimately succumb to a recurrence of the tumor

As Bailey points out, of all brain tumors oligodendrogliomas are the most difficult to identify with certainty in routine histologic preparations. They are most often confused with well-differentiated fibrillary astrocytomas, particularly if the latter have certain edematous and degenerative changes. The best-differentiated variety is composed of sparsely distributed small cells with small, round, dense nuclei. As is true of normal oligodendroglial cells the cytoplasm is refractive to the usual stains so that each nucleus is surrounded by a clear space that gives a so-called "honeycomb pattern." Calcospherites are present in 70 per cent of these tumors and in 40 per cent are sufficiently numerous to be detectable radiologically The more undifferentiated varieties are characterized by the fact that the cytoplasm of the cells is stainable, although very few or no glial fibers can be demonstrated with phosphotungstic acid hematoxylin The cells in these tumors are smaller than the usual cytoplasmic astrocyte the nucleus is more round and dense, and the general cellularity may be more sparse. The distinction of the most malignant types from other types of glioblastomas is apparently impracticable.

Glioblastoma Multiforme.—Glioblastoma multiforme is the most undifferentiated and malignant glial tumor There have been repeated efforts to subdivide this group on the basis of various criteria, but none have resulted in a classification that imparts any significant prognostic information. The tumor occurs at all stages of life from infancy to extremely old age, but the mean age of occurrence is about 48 years Men are twice as frequently affected as women. The majority of the tumors are located in the cerebral hemispheres usually in the posterior extremity of the frontal lobes or the adjacent temporal or parietal lobes. About one fourth extend across the corpus callosum into the opposite hemisphere. The mean duration of symptoms is three months before operation. With present therapeutic methods about a third of the patients do not survive more than a month after operation, and of those who do the mean postoperative survival is six months or less The longest authenticated survival is fourteen years. The only favorable prognostic sign is the early appearance of convulsions in such cases the total duration of life may be about twice that of others. This is probably due to the fact that convulsions arise from involvement of the cortex, and tumors so located give obvious earlier symptoms.

Grossly these tumors are characterized by their variegated appearance. They usually have poorly delimited borders of firm gray tissue and central areas of hemorrhage, yellow necrosis, and cysts. Multiforme is as appropriate a term for the gross characteristics of individual tumors as it is for comparison of the clinical, gross, and histologic qualities of different tumors of this class.



Figs 989-992.—Glioblastoma multiforme four characteristic features as illustrated by different tumors

Fig. 989.—Necrosis with pseudopalisades of nuclei H and E. stain (×280.) (W U neg. 52-4256.)

Fig 990.—Hypertrophy and hyperplasia of the endothelial walls of blood vessels. H and E. stain. (×280.) (W U neg 52-4257.)

Fig. 991.—Giant cells. H and E. stain (×280.) (W U neg 52-4254.)

Fig 992.—Mitotic figures. H and E. stain. (×280.) (W U neg 52-4255.)

Histologically there are four common characteristics of glioblastomas as well as several basic cellular patterns. These common characteristics are really qualities of anaplasia, and the basic cellular types although rarely pure can often be recognized as caricatures of the patterns of the astrocytomas and ependymomas. The first of these characteristics is the presence of foci of pyknotic cells in a pattern that has been called pseudopalisades. A second characteristic is the presence of numerous and bizarre mitotic figures. Third there are often giant cells that are true multinucleate neoplastic forms. The number of these cells is greatest in those tumors which are apparently malignant cytoplasmic astrocytomas, and they sometimes have huge striking eosinophilic nucleoli resembling viral inclusions but which are not accompanied by the other typical changes in the chromatin of the nucleus. The final characteristic is a hypertrophy and hyperplasia of the vessels of the tumor so that great thick tubes and masses of endothelium are formed in some instances, and in others there is a numerical increase and higher concentration of vessels of more normal appearance. This quality is apparently a basic response of the vessels of the brain to rapid neoplastic growth for it is also seen occasionally in other gliomas and even with metastatic carcinoma in the brain. The degree or prominence of each of these characteristic features of the glioblastoma has no significant effect on its biologic behavior

Medulloblastoma.—Medulloblastomas are a strange and individual group of tumors. The diagnosis has been widely used in many series of cases yet there is a present tendency to separate certain tumors as ependymomas and primary sarcomas from those that were formerly assigned to this group What remains is a tumor with a relatively constant histologic structure and usually a characteristic clinical picture. The tumor occurs in children usually between the ages of 2 and 7 years, and is much more common in boys than in girls. It is located in the cerebellum, usually in the midline. Cases of similar tumors that do not fit these specifications usually do not correspond exactly in their histologic structure and probably belong in another category *Grossly the tumors are pink and fleshy* and often poorly delimited. Evidence of spread in the subarachnoid space is typical but can be seen with other rapidly growing gliomas that reach the surface of the ventricles or break through the pia. Microscopically the medulloblastoma is a highly cellular mass of dense small, round nuclei with coarse patterns of chromatin and practically no visible cytoplasm. The latter when present, is only a short stub on one side of the cell that gives it a "carrot-shaped" outline. Mitotic figures may be frequent but are often difficult to identify The most characteristic pattern is probably a continuous sheet of cells interrupted by variable amounts of vascular stroma. Although rosettes are often mentioned in descriptions of these tumors they probably indicate that the tumor is an ependymoma. The general appearance is histologically identical with the more uniform and less well differentiated peripheral neuroblastomas and retinoblastomas

The origin and nature of this tumor are very much in question. It is significant that Bailey and Cushing in their original description admit the name itself was a compromise spongioblastoma was pre-empted by Globus for the tumor now referred to as a glioblastoma, so the hypothetical term of medulloblastoma

was coined in compromise Since then meduloblasts have been described in various sites in embryonic and adult brains particularly in the region of the anterior medullary vellum Some authors describe neuroblasts of various degrees of differentiation in these tumors others point to the infantile external granular layer of the cerebellum and still others dismiss consideration with the concept that they are tumors *sui generis* Regardless of the viewpoint taken the existence of these tumors with their characteristic clinical qualities and more or less characteristic histologic structure is indisputable

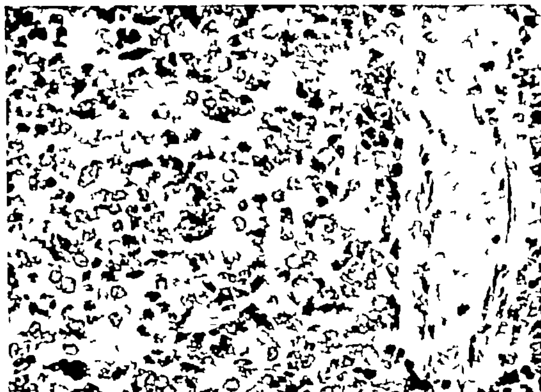
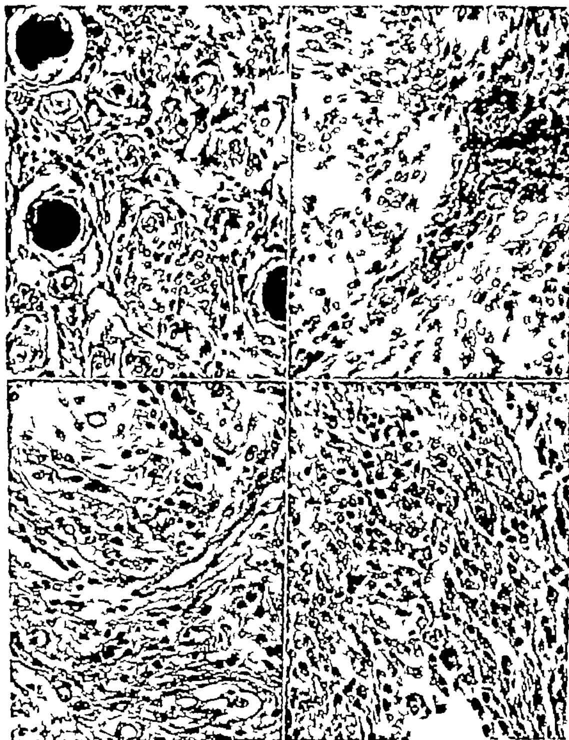


Fig. 993.—Medulloblastoma. H and E. stain. (×750.) (W U neg 5?-4238.)

Medulloblastomas are generally considered to be the most radiosensitive of the glial or central neurectodermal tumors. The prognosis, nevertheless is very poor and Grant observed that no patient with this tumor who developed symptoms before the age of 7 years survived beyond the fifth postoperative year Hydrocephalus or compression of the spinal cord due to subarachnoid metastases is often a feature of the recurrence of these tumors.

Ganglioastrocytoma.—Ganglioastrocytomas have been described as tumors in which recognizably malignant neurons are present. The stroma of these rare tumors is that of an astrocytoma, and its degree of differentiation is apparently the determining factor in its behavior

Roentgenologic Therapy of Gliomas.—Irradiation therapy of glial tumors in general has proved to be very disappointing Sufficient irradiation to cause extensive changes in the stroma of the brain and even death of neurons has not successfully eliminated tumors of the glioblastoma type. Lindgren has reported that about one third of all glial tumors to which he had administered intensive



Figs. 994 997 —Meningioma logic types.

Fig 994 —Meningothelial w orls and psammoma and E stain. (×280) (W U neg 49-3364)

Fig 995 —Meningothelial w whorls. H and ?80.) (W U neg 52-426)

Fig 996 —Meningothelial wit a. H and E. s) (W U neg 5?-4263)

Fig. 99 alignant" meni and E. stai (W U ne 52-4264)

fibromas plus small collections or diffusely scattered meningothelial cells Occasionally the predominant tissue is composed of hyaline blood vessels from the stroma Calcified spherites called psammoma bodies may be very numerous rare or absent they are more characteristic of the meningiothelial meningiomas with tight whorls None of these different histologic characteristics have any bearing on the benign course of most meningiomas

About 10 per cent of meningiomas have mitotic figures atypical forms of cells and their nuclei and sufficient anaplasia to justify placing them in a separate subcategory These tumors seem to have a more rapid growth and all other things such as size and position being equal are the most difficult to eradicate. For lack of a better name these have been called malignant meningiomas" and they carry an average life expectancy of one to two years The remainder of meningiomas are benign tumors that are curable if they can be completely removed. They can be transplanted but they never metastasize Invasion of the tumor into the overlying hyperostosis does not have the general significance of invasion of a foreign tissue by a tumor and if the involved bone is removed the prognosis remains equally favorable

Tumors of the meninges that are essentially fibrosarcomas or hemangioendothelial sarcomas have been referred to as sarcomatous fibroblastic meningiomas and angioblastic meningiomas respectively Fisher has suggested that some of these tumors are hemangiopericytomas. Many are malignant with the biologic characteristics of their counterparts that arise in other tissues of the body The fibrosarcoma of arachnoid origin probably accounts for most of the intracranial tumors that spontaneously escape the confinement of the skull.

Meningiomas comprise over a fourth of intraspinal neoplasms They are of intradural and extramedullary position and almost four fifths occur in the thoracic region. The spinal tumors carry the same hopeful prognosis as their intracranial *homologues*

There are occasional rare melanotic tumors of the central nervous system. They arise from pigmented cells in the pia arachnoid that like the meningothelial cells are derived from the neural crest Although the question is often raised as to whether a malignant melanoma may have arisen in the central nervous system, only about 10 per cent of the reported cases suggest that a primary meningeal pigmented tumor was a true melanoma and could metastasize. The remainder are apparently more comparable to the pigmented nevi of the skin. Foot has commented upon the resemblances of these pigmented tumors of the meninges to both meningiomas and nevi which is not surprising considering the present concepts of histogenesis of both of these tumors

Neurilemoma and Tumors of the Cerebellopontine Angle.—Intracranial and intraspinal neurilemomas arise most often on the auditory nerve or more properly its vestibular branch and the posterior roots of spinal nerves. They may occur on any cranial nerve except the olfactory or the optic. They comprise about 10 per cent of intracranial tumors and almost a third of intraspinal tumors. The biologic and histologic characteristics of these tumors as to their ages of occurrence multiplicity relationship to von Recklinghausen's disease etc. are the same

as those of the similar tumors of peripheral nerves. As tumors of Schwann cells they arise only from those portions of the nerves with the peripheral type of myelination. The zone of transition or Obersteiner Redlich zone between central and peripheral myelin patterns is apparently the most vulnerable. Because this zone of the auditory nerve lies at a considerable distance from the surface of the brain stem and within the internal auditory canal certain characteristics of these eighth nerve tumors such as early involvement of the facial nerve and widening of the internal auditory meatus, detectable by roentgenograms are easily understood

Treatment of these tumors is beset with difficulties from the standpoint of the approach to and structures about them. Anything short of total excision leads to recurrence, but it is often technically impossible to accomplish this goal because of the surprising size of some of these tumors and their intimate adhesions to blood vessels and other cranial nerves. Interruption of vital arterial supply to the tegmentum of the pons is a hazard of the operation

Gliomas of the cerebellopontine angle are rare tumors that are sometimes discovered when a neurilemoma is expected They arise in the extra axial position from the glial lamina of the lateral recesses of the fourth ventricle and are consequently often ependymomas or astrocytomas. Because they are not as intimately associated with the auditory nerve as neurilemomas, total loss of hearing may not be part of the clinical syndrome. Another possible source of extra axial gliomas is found in the small glial heterotopias that are rather frequently observed in the subarachnoid spaces about the brain stem in routine postmortem studies.

Primary Intracranial Sarcoma.—The diagnosis of primary intracranial sarcoma has been neglected in the thirty five years since Bailey and Cushing established the glial nature of most tumors of the brain, probably in compensation for previous abuse of the diagnosis. In addition to the meningeal fibrosarcomas described with the meningiomas there occur within the brain itself certain tumors derived from tissues of the mesenchyme These include tumors of reticuloendothelial cells with histologic patterns like those of reticulum-cell sarcoma or Hodgkin s disease. They can be considered tumors of microglia or of cells from about the cerebral blood vessels. Many of these tumors rather characteristically involve the deep portions of the frontal lobes and diencephalon. Since only occasional examples of these tumors have been described little can be said of their characteristics except that they appear to be similar to other lymphomas.

There are also highly cellular tumors of the cerebellum of children and cerebrum of young adults that contain sparse but definite networks of reticulin fibers and are consequently of mesenchymal origin They tend to occur in older children and in general are atypical tumors that have probably been classified as medulloblastomas in most instances. The cells often have elongated nuclei and definite amounts of fibrillary cytoplasm that give them fusiform shapes. These tumors may be as common as true medulloblastomas but their clinical and pathologic pictures have not yet been fully defined There is some suggestion that they include the tumors which have been reported as metastasizing medulloblastomas. It is a clinical impression that patients with this tumor have a slightly better prognosis than those with medulloblastoma.

Other primary sarcomas such as fibrosarcoma and perithelial sarcoma are occasionally encountered, principally in patients in the fourth, fifth, and sixth decades.

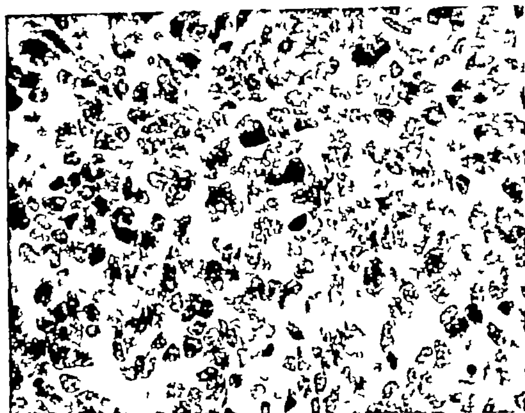


Fig 998 — Primary intracranial sarcoma from the cerebellum of a child special preparations were positive for reticulin Compare with Fig 993 H. and E stain. (×750) (W U neg 52-4239)

Metastatic Tumors

Metastatic tumors of the central nervous system are of importance to the neurosurgeon as problems in differential diagnosis and because the manifestations of a metastatic tumor in the central nervous system may be so prominent that appreciable comfortable life can be salvaged by its removal. Most neurosurgeons report that about 4 per cent of the intracranial tumors on which they operate are metastatic in origin but in some large general autopsy series as many as 27 per cent of all tumors involving the central nervous system are of metastatic origin. Most are carcinomas largely because carcinomas are more common tumors. Actually a high percentage of sarcomas spread to the central nervous system. Figures on the percentage of all tumors that metastasize to the brain are largely individual estimates and vary from 4 to 9 per cent From a third to one half of all carcinomas of the lung about one seventh of carcinomas of the breast and as many as half of malignant melanomas spread to the central nervous system while the incidence for carcinoma of the stomach is about 3 per cent and for carcinoma of the prostate, 4 per cent The lung the gastrointestinal tract, the breast the kidney and melanoma of the skin are the source of two thirds to four fifths of

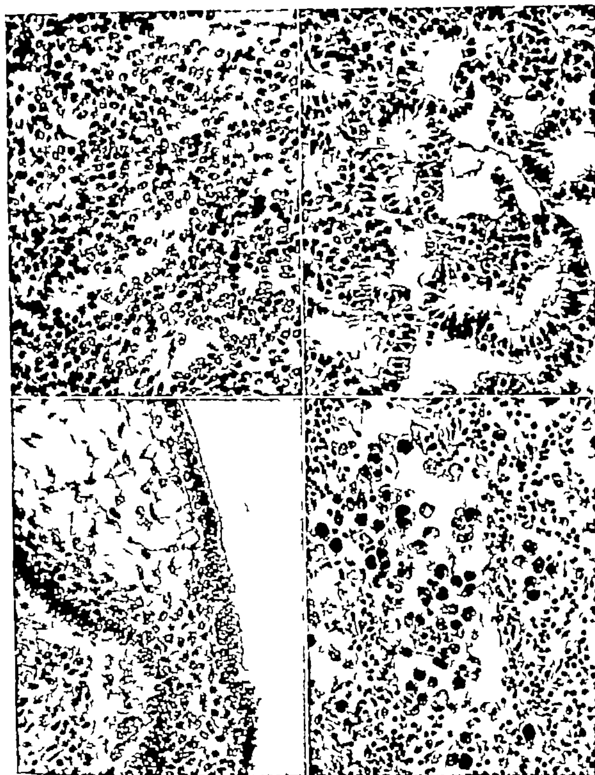
metastatic tumors in the central nervous system with the lung alone supplying about a quarter The colon is the most frequent primary site of the metastatic tumors from the gastrointestinal system with the stomach second most common. From a tenth to a quarter of metastatic tumors in different series arise in the breast, while renal carcinoma and malignant melanoma are each rather constantly reported as about one tenth of such lesions. About one tenth of all primary tumors with distant metastases have secondary tumors only in the central nervous system and of these more than half are bronchogenic carcinomas. The distribution of metastatic lesions in the central nervous system is proportional to the size and blood supply of the particular portion under consideration. In approximately two thirds of cases the lesions are multiple by the time death supervenes and the percentage is probably almost as high at the time symptoms first develop

Tumors of Special Tissues

Pituitary —Tumors of the pituitary have formed variable proportions of the intracranial tumors seen by different surgeons Cushing was very interested in diseases of this gland and its tumors comprised 17 8 per cent of his series. Other surgeons have seen considerably fewer, the usual experience being probably in the neighborhood of 10 per cent The tumors of this gland are of three classes the adenomas, the craniopharyngiomas and incidental tumors of this region. They are found in all age groups with more adenomas in patients in the fifth and sixth decades the craniopharyngiomas usually in children and young adults, and the gliomas and sarcomas so rare that no conclusions can be drawn as to their characteristic occurrences Most of these tumors produce symptomatology by pressure upon and atrophy of the remaining pituitary pressure upon the optic tracts and chiasm, and pressure upon the floor of the third ventricle and hypothalamus.

The true adenomas of the pituitary are of three types acidophilic, basophilic, and chromophobic. The acidophilic adenomas occur about twice as frequently as the basophilic, and the chromophobic about three or more times as frequently as all the chromophilic The acidophilic adenomas are functional tumors that are associated with gigantism or acromegaly The cells are arranged without particular pattern on a fibrovascular stroma. The cells themselves are typical acidophils but their positive identification can be made only with the aid of special mordanting and staining with azure, aniline blue and orange G It is usually easier to make a diagnosis of an acidophilic type of adenoma from looking at the patient than from ordinary histologic slides In older tumors the amount of acidophilic granulation of the cells may be greatly reduced. Basophilic adenomas of the pituitary although intimately connected with the endocrine problems of Cushing's disease, practically never attain sufficient size to give the manifestations of a tumor

Chromophobic adenomas of the pituitary present a wide range of histologic pictures. Most are soft masses of reddish tissue composed of small irregular cells with dark cytoplasm that stains bluish with hematoxylin. The nuclei are usually small, round, and very dense. There are varieties, however that range from frankly epithelial patterns through ribbons of palisaded fusiform cells that Kraus



Figs. 999-1002.—Intracranial tumors of special tissues.

Figs. 999 and 1000.—Two histologic patterns in chromophobic adenomas of the pituitary. H. and E. stain. (×280.) (W.U. negs. 52-4265 and 49-3365.)

Fig. 1001.—Craniopharyngioma in the pattern of an adamantinoma. H. and E. stain. (×280.) (W.U. neg. 52-4266.)

Fig. 1002.—Pinealoma. H. and E. stain. (×280.) (W.U. neg. 52-4267.)

has called a fetal cell adenoma to patterns that resemble those of a cellular ependymoma and have been interpreted as such. Kernohan and others prefer the terms diffuse, sinusoidal, and papillary as descriptive of these various types. As far as is known, none of these histologic patterns bears a special significance for prognosis. The therapeutic approach to these lesions varies in different clinics. Progressive encroachment of the tumor on the optic pathways usually requires operative intervention Horrax has recently reported that newer methods of radiotherapy by which 4,000 roentgens can be more conveniently delivered to the adenoma have resulted in decreasing the necessity for operation from 58 per cent to 18 per cent of cases.

Some histologic patterns in adenomas with irregular cells and nuclei have been referred to as carcinoma of the pituitary but aside from the fact that some tumors break through the diaphragm sellae and into the cavernous sinus and adjacent structures they do not possess the biologic characteristics of most other true carcinomas. The term malignant adenoma has been suggested as being more appropriate than carcinoma for these tumors

Craniopharyngiomas are tumors derived from pharyngeal anlage that are misplaced in the evolution of Rathke's pouch They are usually cystic tumors, and their histology is typically very similar or identical to that of the adamantinoma of the jaws. Many however lack such features as the peripheral vacuolization of the palisaded layer of cells around the islands of stellate cells and there is often a high proportion of stratified squamous epithelium. Epidermoid cysts also occur in this same site and, although Kraus suggests they may be of a different embryologic origin there are tumors that appear to combine histologic features of both types of lesions. A rare epidermoid carcinoma also arises in this region.

Most patients with craniopharyngiomas are less than 20 years of age, but many do not develop symptoms until the fifth or sixth decade The incidence is about equally distributed between males and females. Symptoms are dominated by those of hydrocephalus, especially in the younger patients and of pressure upon the chiasm and optic tracts. Signs of hypothalamic involvement such as diabetes insipidus are common. About two thirds of cases show calcification in the tumor and three fourths an abnormal sellar outline by roentgenographic examination. Complete excision is curative but operation is hazardous because of the dangers of injury to the hypothalamus. Incomplete removal is followed by a slowly recurrent growth of the tumor Irradiation is not considered beneficial.

Pineal.—The region of the pineal body is the seat of three special types of tumors epidermoid inclusion cysts, teratomas and a characteristic tumor that may well be referred to as a pinealoma. Its microscopic resemblance to the embryonic structure of the pineal has been remarked upon, but its essential histologic identity with seminomas and dysgerminomas has suggested to Russell that it is really a teratoid tumor Like the gonadal tumors, its microscopic structure consists of large cells with large clear nuclei and pale cytoplasm that are more or less sharply divided into a mosaic by a light stroma infiltrated by cells with the appearance of lymphocytes. There also occurs a scattering of cysts and glial tumors of this body that have been referred to as pineal ependymomas and pineal spongioblastomas.

Pinealomas characteristically arise in patients between 15 and 25 years of age, and 88 per cent occur in males. The special symptomatology derives from pressure of the tumor upon the regions at the rear of the third ventricle and over the mesencephalon. Oculomotor and visual disturbances are therefore prominent. Diabetes insipidus or other evidence of some endocrine imbalance is present in less than half the patients. Pubertas praecox sometimes occurs in these patients most likely because of pressure effects on the third ventricle For some unknown reason its incidence with pinealomas appears to be less frequent than in cases of teratoma of the pineal The site of these tumors is very difficult to approach surgically and operative results have been disappointing The characteristic pinealoma is quite radiosensitive so that alleviation of symptoms can be obtained by radiotherapy teratomas and cysts on the other hand are but little affected

Teratoma —The rare occurrence of teratomas of the central nervous system need only be mentioned. They have a predilection for arising in midline sites such as the pineal and pituitary regions and in the spinal cord. Most cases occur in children or young adults. The only histologic feature that is different from other teratomas is the often prominent portion of the tumor that is composed of tissue resembling various developmental stages of the central nervous system. Immature neuroectoderm is sometimes so prominent that the tumor may be called medulloepithelioma until further search reveals the other tissues of the teratoma. Primary intracranial chorioepithelioma occurs as a variety of this tumor The intracranial teratomas are usually rapidly fatal those in the spinal canal are often slowly growing tumors of adult tissues that behave more like congenital malformations. Only 7 of 40 infants and children with sacrococcygeal teratoma at the Boston Children's Hospital developed distant metastases.

Colloid Cyst.—Colloid cysts of the third ventricle are classified by some as deformities of the choroid plexus and by others as cystic remnants of the paraphysis. They are always attached in the anterior part of the third ventricle, either to the root of the choroid plexus or the anterior wall. The cyst has only one cavity filled with thick fluid that may be clear or so cloudy from cholesterol crystals and foam cells that it resembles pus The wall is lined by low cuboidal epithelium that is usually only one layer thick and may occasionally be ciliated. Beneath this is a thin layer of fibrous tissue. The cysts vary in size to over 2.5 cm. in diameter, but those smaller than 1 cm. rarely give symptoms The age of onset of symptoms varies greatly rarely appearing in patients under 15 years of age, and often appearing in patients in the third and fourth decades. The symptoms are those of an acute hydrocephalus sometimes intermittent due to blockage of the foramen of Monro and local effects on the third ventricle and optic tracts. Unlike other intraventricular tumors it does not cause increased protein in the cerebrospinal fluid Death from acute hydrocephalus occurs unexpectedly in 20 per cent of untreated patients Operative removal of the cyst results in relief of almost all symptoms except those due to permanent damage of neighboring structures.

DISEASES OF MUSCLE

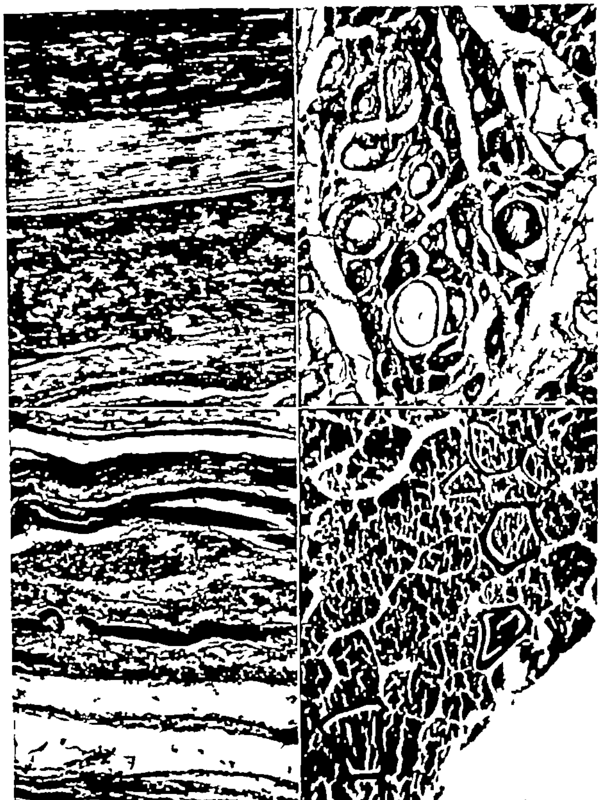
The surgical pathology of muscular diseases consists almost entirely of diagnostic biopsies. These are capable of yielding information which is of consider

able categorical importance in differential diagnosis and is sometimes specifically diagnostic. Muscle biopsies are often combined with biopsy of the skin and sometimes of nerve in the same procedure to considerable advantage in interpretation of the case. Care is especially important to obtain good fixation without excessive contraction or distortion of the muscle fragment. This may be done by spreading the tissue on cardboard or thick paper before immersion in the fixative. Ideally at least two sections should be made to show muscle fibers in cross section as well as longitudinal section. Special staining with Masson's trichrome or phosphotungstic acid hematoxylin as well as hematoxylin and eosin is often advantageous.

From the standpoint of histologic reactions muscle diseases may be divided into five main categories (1) atrophies, which are usually due to the loss of nerve supply in some manner (2) dystrophies, which appear to be primary degenerative diseases of the muscle cells (3) inflammations, which may be of a special type characteristic of muscle or of types that are similar to those seen in other tissues (4) traumatic and circulatory disturbances and (5) disorders of function which do not result in significant or characteristic changes in microscopic structure of the muscle. The neoplasms of muscle are discussed in other chapters and consist of rhabdomyosarcomas, possibly the granular cell myoblastoma, and tumors of blood vessels and connective tissue that form the investments of muscles.

Spinal and Neural Muscular Atrophies

Skeletal muscle fibers hypertrophy with exercise and decrease in diameter and volume with disuse. Such atrophic changes are particularly pronounced if a fiber is denervated and loses its tonic stimuli. The normal size of muscle fibers varies in different muscles as well as with the age and physical development of the individual most muscles of the extremities have fibers that average about 50 microns in diameter while external ocular muscles regularly contain uniformly small fibers of 20 to 25 microns in diameter (Greenfield) The muscles in diseases characterized by pathologic atrophy contain fibers that are reduced to 20 microns or less in diameter yet which retain normal structural features such as cross striations. The sarcolemmal nuclei may increase slightly in size and their nucleoli become more prominent. Combined with the decreased fiber size this results in a considerable apparent increase in the number of nuclei although it is not certain there is any absolute increase of nuclei. The most characteristic feature of biopsies from patients with diseases of this type consists of large groups of these small atrophic fibers with persisting islands of smaller groups of normal or hypertrophied fibers. This grouping is considered to be due to the atrophy of fibers by motor units as their anterior horn cells or major nerve fibers are destroyed. It is not until late in these diseases that structural changes in the atrophied fibers and interstitial tissue occur Sarcoplasm and myofibrils may disappear sometimes with persistence of rows of sarcolemmal nuclei, and finally fibers are completely destroyed. Interstitial connective tissue increases slowly in amount and there may be moderate infiltration of fat cells into the fasciclea. Cellular infiltrations in the inter



Figs 1003-1006 —Four patterns of reaction in primary diseases of muscle (U Va. neg 6308)

Fig 1003 —Fascicular atrophy in amyotrophic lateral sclerosis H and E stain (×125)

Fig. 1004 —Dystrophy with irregular large hyalinized fibers. H and E. stain. (×125)

Fig. 1005 —Polymyositis with disrupted fibers and heavy cellular infiltration. H and E. stain. (×125) (Courtesy Dr C E Wheeler)

Fig. 1006 —Ringed fibers as occur in myotonic states, especially myotonic dystrophy Masson stain (×260) (Courtesy Dr A. G Smith.)

stitial tissues and regenerative proliferation of fragments of muscle fibers form no part of the histologic pattern in these muscles.

This group includes diseases with primary lesions in the spinal cord such as amyotrophic lateral sclerosis ("motor neuron disease") amyotonia congenita (Oppenheim) infantile progressive spinal muscular atrophy (Werdnig Hoffmann) and poliomyelitis, as well as diseases of peripheral nerves such as peroneal muscular atrophy (Charcot Marie Tooth) chronic hypertrophic polyneuritis (Déjerine Sottas) diabetic polyneuritis with muscular atrophy and peripheral neuritis in diseases such as polyarteritis nodosa If the peripheral nerve is completely interrupted, the muscle will be atrophic in all parts and not show fascicular atrophy but only a portion of axonal fibers are destroyed within the nerve in most diseases short of traumatic severance. If a muscle is denervated completely, atrophy is appreciable within *three months* but it requires about *eleven months* for significant interstitial fibrosis to appear The specific lesion affecting the nerves and causing the muscular atrophy can often be recognized in the biopsy in such diseases as polyarteritis.

Muscular Dystrophies

These disorders have been divided into many eponymic clinical syndromes which are grouped by Adams into four types (1) severe generalized familial muscular dystrophy (2) mild restricted muscular dystrophy (3) progressive dystrophic ophthalmoplegia and (4) myotonic dystrophy Particularly in the first two of these groups it is characteristic for muscles of the trunk and shoulder or pelvic girdle to be affected early Hereditary features and biochemical evidence of abnormal muscle metabolism as well as anatomic and physiologic evidence that the nerves to affected muscles are intact establish this disease or these diseases as primary disorders of the muscle cells With the exception of certain features of the myotonic syndromes, the pathologic histology is the same in all the various clinical divisions of this group Adams has emphasized the absence of regenerative activity in these diseases especially in separating them from the inflammatory or polymyositis group

Enlarged fibers occurring singly and showing hyalinization, loss of striations, and granular or floccular changes are the central characteristics of dystrophic muscles. The sarcolemmal nuclei are swollen and increased in number In addition many other fibers are of small size and some fibers show splitting With complete destruction the only remaining elements of the muscle fibers may be a chain of nuclei. There is a relatively early infiltration of muscle fascicles by adipose cells and fibrous connective tissue, and in late stages these elements may almost completely replace the muscle. Adams states that phagocytosis of degenerating fibers, significant cellular infiltrations and muscle buds with giant or multiple nuclei and basophilic cytoplasm are not part of the reaction of dystrophy From a practical standpoint however it seems difficult to find biopsies from patients with clear dystrophic syndromes which do not contain some element of these changes, although they are not nearly so prominent as is seen in polymyositis. It is interesting and significant that Greenfield in his series of muscle biopsies did not distin-

guish between dystrophies and myositis on purely histologic evidence because of the variations in the quantitative intensity of these changes within the two groups.

Particularly with myotonic dystrophy, muscle fibers will show inward migration of nuclei to a central position and peripheral displacement of bands of striated myofibrils so that the major portion of the fiber is encircled by fibrils running almost at right angles to the axis of the fiber. Some fibers may also contain large masses of sarcoplasm beneath the sarcolemma that are devoid of myofibrils. These changes, central nuclei, sarcoplasmic masses and "ringbinding" can be found in many conditions; rare examples are seen in supposedly normal muscle (Perry, Greenfield). Combined and in fair numbers however they seem fairly typical of myotonic dystrophy.

Myositis

Inflammatory diseases of muscle can be divided into two groups. The first includes those due to recognized etiologic agents such as bacteria and parasites. The pathologic alterations in this group are complex and variable but are of the nature that would be expected from one's knowledge of the general pathology of these diseases. The second group has been called polymyositis and may be subdivided into acute and chronic forms (Adams). Theses diseases appear to be related in some ways to the so-called collagen diseases and are of unknown etiology. Certain of their clinical and pathologic manifestations are similar to those of a dystrophy and the differential diagnosis is often facilitated by biopsy.

Acute polymyositis may be combined with lesions of the skin, in which case it is called dermatomyositis, or with evidence of involvement of nerves, when the term neuromyositis may be applied. The muscles show intense inflammation that is expressed by granular and floccular degeneration, fragmentation and phagocytosis of muscle fibers, interstitial infiltrations of macrophages, and even some granular leukocytes. In addition there are changes interpreted as regenerative which consist of buds or separate masses of basophilic sarcoplasm in which there are central large or multiple nuclei. This disease may be overwhelming and fatal, but the majority of cases recover.

Chronic polymyositis on the other hand is a more relentlessly progressive disease. The histologic appearance of the muscles may be that of intense inflammation even late in the course of some cases, but in many the changes consist of a greater interstitial fibrosis with less inflammatory cellular infiltration and evidence of regenerative reaction by the muscle fibers. Adams emphasizes the particular atrophy, vacuolation, and destruction of fibers at the periphery of muscle fascicles in this condition. It may progress to complete destruction of the muscle and fibrous contracture.

Nodular interstitial infiltrations, particularly of lymphocytes, are seen in muscles in various diseases such as myasthenia gravis, rheumatoid arthritis and thyrotoxicosis. The term lymphorrhages has been used for these lesions especially those of myasthenia gravis and Greenfield emphasizes the compactness of the infiltrate between undamaged fibers as being of specific significance in that disease. The thymus in myasthenia gravis may be the seat of a thymoma in 15 per cent of patients and shows a microscopic abnormality in about 80 per cent (Castleman).

Degenerative changes, usually in isolated muscle fibers, are found in a number of infectious and toxic diseases. These apparently are not due to the effect of any specific etiologic agent present in the muscle. They include granular and floccular changes and hyalinization, one type of which is Zenker's hyaline degeneration. Because of the nature of the diseases in which these changes occur, specimens are not so frequently seen in the surgical pathology laboratory as at autopsy

Traumatic and Circulatory Disturbances

Several interesting reactions may arise in muscle as the result of hemorrhage or ischemia Myositis ossificans has been discussed in a previous chapter The sternomastoid tumor of infancy which leads to torticollis and Volkmann's contracture which may complicate the application of casts or bandages too tightly are thought to result from ischemia due principally to interruption of the venous drainage. Both of these lesions contain large amounts of cellular fibrous tissue within an otherwise destroyed muscle, of which only a few fibers may eventually persist. Violent contraction or hard exercise in the untrained may lead to rupture of muscle sheathes with herniation or hemorrhages in the muscle. A particularly interesting form is the "anterior tibial compartment" syndrome where initial edema or hemorrhage increases the volume of a rather rigidly confined muscle and results in progressive destruction of the remainder of the muscle apparently by ischemia. The connective tissue in these muscles reacts rapidly with the formation of considerable fibrosis.

Muscular Disorders Without Anatomic Change

Diseases of a physiologic or functional disarrangement of muscle excitability and the transmission of neuromuscular stimuli often show no evidence of anatomic changes in the muscle fibers. Myasthenia gravis, except for the rather incidental lymphorrhages belongs to this group, as do periodic paralysis, myotonia congenita (Thomsen's disease) tetanus, and botulism.

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Chapter 26

SURGICAL PATHOLOGY OF THE EYES AND OCULAR ADNEXA

L. E. Zimmerman, M D

EYELIDS

- Developmental Anomalies
  - Accessory Caruncle
  - Dermoid Cysts
  - Nevi
  - Angiomas
  - Neurofibromas
- Inflammations
  - Chalazion
  - Vernal Conjunctivitis
  - Trachoma
  - Granuloma Pyogenicum
- Metabolic Disorders
  - Xanthomatosis
- Degenerative Processes
- Cysts
  - Cysts of Moll's Glands
  - Hidrocystomas
  - Sebaceous Cysts
- Neoplasms and Tumorlike Lesions of the Lids
  - Neoplasms of the Surface Epithelium
    - Basal Cell Carcinoma
    - Squamous Cell Carcinoma
    - Extramammary Paget's Disease
    - Papillomas
  - Nonneoplastic Keratotic Lesions
    - Pseudoepitheliomatous Hyperplasia
    - Keratoacanthoma
    - Inverted Follicular Keratosis
    - Seborrheic Keratosis
    - Senile Keratosis
    - Cutaneous Horn
    - Benign Keratosis, Type Uncertain
    - Miscellaneous

I wish to acknowledge the assistance of Dr T E. Sanders Ophthalmic Pathologist at Washington University School of Medicine and that of Miss E. V Paul of the Armed Forces Institute of Pathology in the preparation of this chapter

portance to the surgical pathologist. Topography is all important in a consideration of biopsy specimens obtained from the eyes for the correct interpretation and diagnosis often hinges upon a knowledge of the precise position and anatomic relationships of the lesion on the lid on the globe or in the orbit The pathologist should not hesitate to demand a complete description of the lesion before he renders a report. Good clinical photographs illustrating the evolution of a given lesion are also extremely valuable in this regard.

Many of the pathologic processes which involve the lids (e.g tuberculosis, lupus erythematosus sarcoidosis etc.) present no special problems, and, since they have been considered elsewhere in this book they will not be discussed here. Special attention will be given to those lesions which are either peculiar to the lids or which present particular problems in this location. Of necessity this review will focus attention upon those lesions which are most likely to turn up in the surgical pathology laboratory For a more comprehensive coverage, the interested reader is referred to Duke Elder's encyclopedic treatment in the fifth volume of his *Text Book of Ophthalmology*

Developmental Anomalies

Developmental anomalies of the eyelids are numerous and of considerable clinical importance but rarely do they come to the attention of the surgical pathologist.

Accessory Caruncle.—The caruncle which is derived from the lower lid is composed of thick nonkeratinized squamous epithelium containing many mucous cells. Hair follicles and sebaceous glands are numerous and the stroma contains smooth muscle fat, nerve bundles and fibrous connective tissue. Rare aberrant, supernumerary or reduplicated caruncles may be encountered in the upper and lower lids at their nasal ends Because of the multiplicity of tissue elements contained in such lesions, the erroneous diagnosis of dermoid cyst might be made.

Dermoid Cysts.—Dermoid cysts are among the lesions encountered more frequently by surgical pathologists Typically they involve the outer third of the upper lid and brow Most of them represent forward extensions of masses which are primarily intraorbital. Some however are of palpebral origin. Microscopically the cysts are observed to be lined by well-differentiated epidermal and dermal tissues containing all of the usual skin appendages (Fig 1007) The lumen is filled with keratinous debris sebum and hairs. In places where these contents have been extruded into the surrounding tissues a severe foreign body inflammatory reaction may be observed.

Nevi.—Nevi dating from birth may be observed in either the cutaneous or the conjunctival surface of the lids. They tend to be of the junctional or compound type, and like those in other areas they may give rise to malignant melanoma (see p 113) A more diffuse and deeply situated melanotic lesion of the lids is the nevus of Ota. This is a form of extrasacral Mongolian spot involving the face in areas supplied by the first and second branches of the trigeminal nerve (Fitzpatrick Helmick) (Fig 1008) Associated conjunctival scleral and orbital pigmentation is present in many of the cases. This type of nevus occurs more fre-

quently in Orientals and Negroes than in Caucasian Malignant change has been reported but is extremely rare (Dorsey)

Angiomas.—Angiomas are probably the most common of all developmental lid lesions which come to the attention of surgical pathologists They vary widely in character and extensiveness Some are minute superficial lesions confined to the lid others penetrate deeply into the orbit and still others involve the lid only in



Fig 1007 —Dermoid cyst of eyelid and brow The cyst lumen is shown in the upper right corner H. and E. stain. (×55) (AFIP Acc 722706.)





Fig 1008 —Oculodermal melanocytosis (nevus of Ota) *A* This 10-year-old Negro boy was born with unilateral hyperpigmentation of the eye eyelids skin of the face and mucous membranes of the fauces. *B* Enucleation was performed because of extensive intraocular involvement and secondary glaucoma There is massive infiltration of the subconjunctival, episcleral scleral, and uveal tissues by very deeply pigmented melanocytes H and E. stain. (×50) (AFIP Acc 138761)

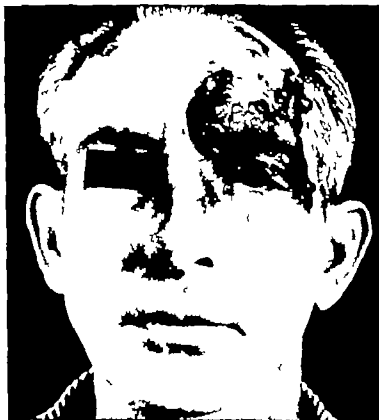


Fig. 1009.—Sturge Weber syndrome. This patient, a 42 year-old white man, had had the facial hemangioma all his life and was blind in the ipsilateral eye because of retinal degeneration, glaucoma and cataract. A choroidal hemangioma was found in the enucleated eye but clinical study failed to disclose evidence of an intracranial lesion (AFIP Acc. 761707) (Courtesy Veterans Administration Hospital, Hines, Ill.)



Fig 1010.—Hemangioma of the choroid in an eye enucleated from a 42 year-old white woman who had had a "port-wine" facial hemangioma since birth and ipsilateral glaucoma since early childhood H. and E. stain (×115) (AFIP Acc 759801)

association with much more extensive portions of the face. Hemangiomas are distinctly more common than lymphangiomas. Microscopically these vascular tumors of the lid present all of the histopathologic variations of those seen elsewhere (see p 850). One variety, the capillary angioma (nevus flammeus or port wine stain) (Fig 1009) is of special interest and importance not only because of its great cosmetic effect but because there may be associated malformations in other tissues (Fig 1010). *In the Sturge Weber syndrome the facial hemangioma may* be associated with a choroidal hemangioma, glaucoma, and a meningeal hemangioma, all on the ipsilateral side (Peterman).

Neurofibromas.—Neurofibromas also may be isolated developmental lesions of the lid or they may be merely a part of von Recklinghausen's neurofibromatosis. Although believed to be present from birth, these tumors frequently show accelerated *growth during childhood or later. When associated with von Recklinghausen's* disease there may be marked asymmetry of the face due to diffuse hypertrophy and pendulousness of all the facial tissues on one side (Fig 1011).



Fig 1011.—Severe unilateral deformity of the face in a patient with von Recklinghausen's neurofibromatosis. (AFIP neg 55 17512.) (Courtesy Dr L. L. Calkins.)

Inflammations

Inflammations of the lids are very numerous. They may be the result of viral, rickettsial, bacterial, mycotic, or parasitic infections, chemical or physical irritants, hypersensitivity states, or systemic dermatologic disorders. Since these inflammatory processes are rarely biopsied they are of relatively little practical significance to pathologists. On occasion, isolated cutaneous lesions of the lids, particularly those that are granulomatous, may be excised either because their appearance suggests carcinoma or for cosmetic reasons. In such cases the pathologists may be the first to recognize that the patient actually has such a systemic disease as blastomycosis, leprosy, sarcoidosis, or lupus erythematosus. Relatively few of these diseases are peculiar to the lids and so their pathologic anatomy presents the same problems in differential diagnosis as encountered in other parts of the body.

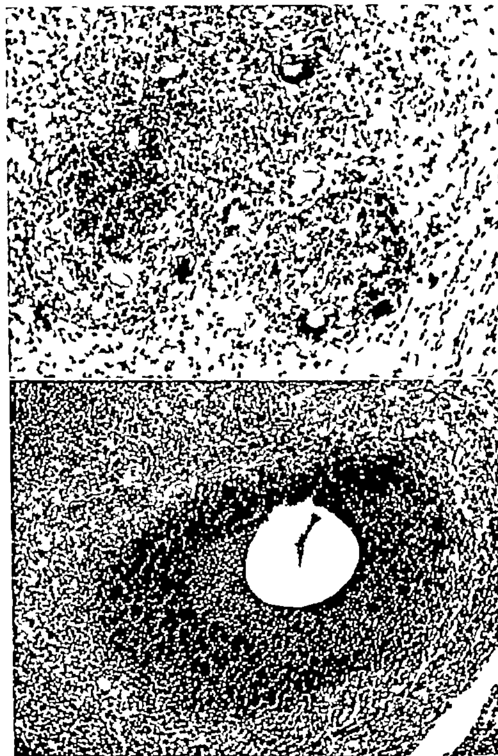


Fig 1012 —Multiple foci of granulomatous inflammation with microabscesses and Langhans giant cells in a chalazion. H. and E. stain. (×137) (AFIP Acc. 91218)

Fig 1013 —The presence of pools of fat in the center of many of the granulomas is characteristic of chalazia. H and E. stain. (×115) (AFIP Acc. 752397)

Chalazion.—This lesion is a distinct exception to what has just been said, for it is not unusual that chalazia are misinterpreted as tuberculous granulomas by pathologists who are unfamiliar with them. A chalazion is essentially a lipogranuloma which develops in and about a meibomian gland, presumably as a consequence of the combined effects of obstruction and nonspecific infection of the excretory passages of the gland. The sebaceous material discharged into the tarsus as a result of the meibomitis provokes an intense granulomatous inflammatory reaction. Although it begins as a deep-seated process, the chalazion not infrequently erupts through the conjunctival surface of the lid. Ordinarily a chalazion is readily recognized and treated, but if after curettage one or more recurrences develop, the clinician should be alert to the possibility of a meibomian gland tumor that



Fig. 1014.—Proliferation of epithelioid cells and giant cells of both the Langhans and foreign body types is particularly noteworthy in this part of the same lesion shown in Fig. 1013. H. and E. stain. (×130.)

has previously escaped recognition. In such cases, excision and histopathologic study are indicated. Microscopically the typical chalazion reveals multiple foci of granulomatous inflammation (Fig. 1012). In the center of many of the focal granulomas there is a small globule of fat, which in paraffin sections presents simply as an empty round to ovoid space (Fig. 1013). Immediately about this is a zone of polymorphonuclear leukocytes and epithelioid cells. Peripheral to this are dense infiltrations of macrophages, lymphocytes, plasma cells, fibroblasts and proliferating capillaries. In some of the older lesions most of the granulomas are of the epithelioid tubercle type (Fig. 1014). When these predominate, the diagnosis of tuberculosis or sarcoidosis may be difficult to exclude.

Vernal Conjunctivitis.—Vernal conjunctivitis (Beigelman) is another inflammatory lesion of the lid with which the pathologist must be familiar, since at times

large polypoid masses of inflamed conjunctiva are excised, either for diagnosis or for therapeutic reasons. Typically the disease is a chronic inflammatory process *affecting young people with springtime exacerbations*. Papillary hypertrophy of the tarsal conjunctiva is the characteristic lid lesion (Fig 1015). The papillae are large with broad flat tops covered by hyperplastic epithelium containing an increased number of mucous cells. Beneath the epithelium the stroma of the papilla contains prominent proliferating blood vessels, fibroblasts, and inflammatory cells, including a large number of eosinophils. With expansion of the stroma of these papillae, extensions of the surface epithelium become trapped beneath and between the papillary projections. The lesions heal with fibrosis and hyalinization.

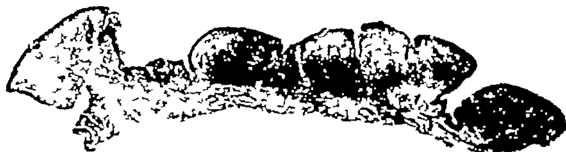


Fig 1015.—Broad flat topped papillae have formed in this chronically inflamed conjunctiva of a patient who had vernal conjunctivitis. H. and E. stain. (×36.) (AFIP Acc. 53660.)

Trachoma.—Trachoma though not a major problem in the United States, continues to be one of the important causes of blindness in certain parts of the world. This of course, is the result of corneal involvement but since the trachoma virus also *infects the palpebral conjunctiva, brief consideration must* be given to the disease here. Early trachomatous lesions stimulate the formation of numerous large lymphoid follicles, in which there are characteristically present many large pale-staining macrophages (Leber's cells) (Fig 1016). Papillary hyperplasia also occurs. One of the most typical and important features of trachoma is the tendency for many minute foci of subepithelial necrosis to stimulate scarring and deformity of the conjunctiva. The destructive inflammatory process frequently extends into the tarsus leading to cicatrization of the meibomian glands, obstruction of the lacrimal gland openings, entropion, and trichiasis. Biopsy material is not often obtained but scrapings are frequently submitted for search for the intracytoplasmic inclusion bodies in the conjunctival epithelium.

Granuloma Pyogenicum.—Granuloma pyogenicum on the lids, like similar lesions on other parts of the body is a rapidly developing fungating mass of granulation tissue. The main problem in differential diagnosis is in excluding a capillary hemangioma which it may mimic.

Metabolic Disorders

Metabolic disorders affecting the lids rarely come to the surgical pathologist's attention. The following is the only important exception

Xanthomatosis.—Xanthomatosis is characterized microscopically by a diffuse proliferation of histiocytes in the superficial corium. The cytoplasm of these cells is tremendously swollen by fine lipoid vacuoles. Giant cells are rarely seen and fibrosis is not usual. Two main clinical forms are observed though their microscopic features are not dissimilar. One is the common xanthelasma or xanthoma planum, the other is the less common but more important xanthoma tuberosum.

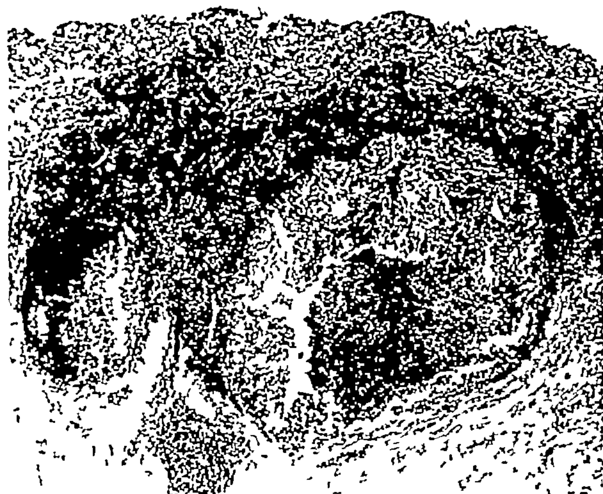


Fig. 1016.—Chronic lymphoid hyperplasia, follicle formation, and reticulum cell proliferation are observed in this case of trachoma. H. and E. stain. (×160.) (AFIP Acc. 33894.) (From Friedenwald, J., et al.: Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, 1952, W. B. Saunders Co.)

The former are slightly elevated plaques located near the inner canthus of upper and lower lids. They are slowly progressive lesions which cause only cosmetic disturbance, tend to occur in middle-aged women, and rarely are indicative of a serious systemic disturbance. Xanthoma tuberosum, however, is a more acutely progressive manifestation of a genetically determined disturbance in lipid metabolism. Hyperlipemia, hypercholesterolemia, and xanthomatous deposits in tendon sheaths and blood vessels may be observed in association with the lid lesions. Similar tuberous lesions may also be seen in diabetes mellitus and in biliary cirrhosis.

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Degenerative Processes

Degenerative processes of importance to pathologists are not common. Several, such as senile atrophy and blepharochalasis, which are associated with a loss of the normal restraining power of the musculofascial layers of the orbit, may permit a herniation of orbital fat. This may be a diffuse process but when localized such herniated masses of fat may be excised and misinterpreted as lipomas.

Cysts

Cysts of the lids may arise from any of the several sweat and sebaceous glands.

Cysts of Moll's Glands.—Cysts of Moll's gland are probably the most frequent. They are generally single slowly progressive and form thin walled transparent vesicles at the lid margin. Although they are generally believed to develop as a result of ductal obstruction the cause of this obstruction probably varies. Microscopically they are simple cysts lined by atrophic cuboidal or flattened epithelial cells (Fig 1017)

Hidrocystomas.—Hidrocystomas are rare, nonobstructive proliferative lesions which involve the lids along with other areas on the face. Microscopically the unilocular or multilocular cyst is observed to be lined by ductal or flattened acinar epithelium of the cutaneous sweat glands.

Sebaceous Cysts.—Sebaceous cysts may arise from the ordinary pilosebaceous glands of the skin or from the more specialized Zeis and meibomian glands located along the lid margin and within the tarsus respectively They are all believed to arise as a consequence of ductal obstruction. Depending upon their age there is usually more or less complete replacement of their sebaceous epithelium by keratinized stratified squamous epithelium (Fig 1018) Inspissated plugs of laminated keratin may fill their lumens Although cystic degeneration of these sebaceous glands is probably a constant feature of obstructing lesions of the lid margins, simple retention cysts that are apparent clinically are not common An associated inflammatory reaction which gives rise to a hordeolum or chalazion characterizes those which are of clinical significance

Neoplasms and Tumorlike Lesions of the Lids

These neoplasms of the lids may be derived from the epidermal or conjunctival surfaces, from the various special adnexal structures below the surface epithelium, or rarely from the stromal elements Among the malignant tumors only the basal cell carcinoma is common, but there are many benign keratotic lesions which give rise to difficulties in the differential diagnosis of squamous cell carcinoma. Most of the lid tumors have their counterparts in other areas and they have already been described in previous chapters, hence they need not be considered in detail here.

Neoplasms of the Surface Epithelium.—These neoplasms include basal cell carcinoma of the skin squamous cell carcinoma of the cutaneous and conjunctival surfaces, Paget's disease, papillomas, and melanomas. Melanomas will be considered separately with other melanotic lesions of the skin and conjunctiva (p. 1002)

Basal Cell Carcinoma—Basal cell carcinoma is by far the most frequent of all true neoplasms arising in any of the palpebral tissues It is of especial importance here because it often tends to invade deeply into the orbit or into the nose The skin surface especially at the inner canthus where so many of these tumors arise is closely applied to underlying bone, muscle, and other important structures Com



Fig 1017—Simple cyst of lid margin believed to be secondary to obstruction of duct of Moll's gland. H and E. stain. (×110) (AFIP Acc. 750918)

Fig 1018—Cyst of lid margin arising in gland of Zeis. There is marked squamous metaplasia of the epithelium which lines the cyst, and the lumen is filled with keratinous debris. H. and E. stain. (×48) (AFIP Acc. 501320)

plications frequently arise as a result of the direct extension of these tumors into such underlying tissues. The problem created by basal cell carcinomas of the eyelid is made even worse by the ophthalmologist's natural inclination to proceed cautiously with therapy in order to minimize surgical or radiation damage to the eye and its adnexa. Because of these factors we see, from time to time basal cell carcinomas which in spite of repeated attempts at local incision, ultimately require an exenteration of the orbit. Even such a radical operation as that may fail to control the tumor's spread, and death is the result of intracranial extension through the orbital or nasal bones.



Fig. 1019—Conjunctival papilloma. Many mucous cells are scattered about in the acanthotic nonkeratinized epithelium. H. and E. stain. (×125.) (AFIP Acc. 230075.) (From Friedenwald, J., et al. Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, 1952. W. B. Saunders Co.)

Basal cell carcinomas arise from the cutaneous surface of the lids and rarely if ever from the conjunctiva. This point is of some diagnostic significance for papillomas of the palpebral conjunctiva may resemble basal cell carcinoma. When such a lesion is excised and sectioned in such a way that its topographic orientation in relation to the conjunctival surface of the lid is not apparent and if the pathologist is not informed of the clinical appearance of the tumor an erroneous diagnosis of basal cell carcinoma can be made (Fig. 1019).

Most basal cell carcinomas of the lids arise at the inner canthus or in the lower lid. They are encountered in all age groups but are more common in the elderly. Histopathologically those arising in the lids show the same variations as those found in other areas (see Chapter on Skin, p. 93). This is true also in regard to their

aggressiveness, for, while some basal cell carcinomas present great therapeutic problems, as already mentioned others are easily controlled by excision or radiation Those of the upper lid and inner canthus carry the worst prognosis, those at the outer canthus the best (Duke-Elder)

Squamous Cell Carcinoma—Squamous cell carcinoma is a much less common lesion in the eyelid—even less in our opinion than Martin s figure of 10 per cent of all lid epitheliomas would suggest Many of the lid lesions submitted to the Registry of Ophthalmic Pathology as squamous cell carcinomas have been regarded by the Armed Forces Institute of Pathology staff as nonneoplastic lesions (see p 994) True squamous cell carcinoma of the eyelid is a potentially serious lesion



Fig 1020—Pagetoid involvement of the skin of the eyelid in a case of meibomian gland carcinoma. H. and E. stain. (×115) (AFIP Acc. 804889)

because of its tendency to lymphatic permeation and distant metastasis This tumor usually arises in a "precancerous" lesion such as senile keratosis, arsenical keratosis or xeroderma pigmentosum and it develops more frequently in persons who have sustained long and repeated exposure to the sun and wind

Extramammary Paget s Disease—This disease of the eyelid is a rare form of lid cancer Some authorities believe that only carcinomas of apocrine sweat glands produce pagetoid lesions in the overlying skin Moll s glands are considered apocrine sweat glands, and Paget s disease of the eyelid has been reported as a feature of carcinoma of these glands (Whorton) Similar intraepithelial extension of glandular carcinoma into the overlying epidermis may be observed with carcinoma of the meibomian gland which is a sebaceous gland (Fig 1020)

Papillomas—Papillomatous lesions of the lids include true squamous papillomas and such other lesions as seborrheic keratosis, warts, and cutaneous horns True

papillomas may arise from either the cutaneous or the conjunctival surface of the lids. The former tend to have a moderately thick layer of keratin over the fronds and deep within the cryptic spaces between fronds (Fig 1021) while the latter are devoid of keratin but contain large numbers of goblet cells interspersed among the proliferating conjunctival squamous cells (Fig 1019)



Fig. 1021 —Squamous papilloma arising from the cutaneous surface of the eyelid There is marked thickening of the granular layer the surface is heavily keratinized, and mucous cells are absent. H. and E. stain. (×24) (AFIP Acc. 292125) (From Friedenwald, J., et al. Ophthalmic Pathology: An Atlas and Textbook Philadelphia 1952 W B Saunders Co)

Nonneoplastic Keratotic Lesions.—These lesions of a variety of types occur frequently on the lids. Some of these may resemble squamous cell carcinoma so closely that even experienced clinicians and pathologists have much difficulty in differential diagnosis

Pseudoepitheliomatous Hyperplasia.—Pseudoepitheliomatous hyperplasia is a term that has been applied to many such cutaneous lesions particularly to those that are secondary to chronic infectious processes such as blastomycosis tuberculosis, syphilis and leishmaniasis (all of which may produce lesions of the lids) Other causes are insect bites, foreign bodies, and certain drugs (e.g., bromides and

iodines) In pseudoepitheliomatous hyperplasia there is usually considerable evidence of a long-standing inflammatory process which has been the stimulus to epidermal proliferation Irregularly elongated rete pegs penetrate deep into the lid and, when these are cut at various angles, they may appear to be infiltrating nests of cancerous tissue (Fig 1022) Generally the degree of dyskeratosis and



Fig 1022.—Pseudoepitheliomatous hyperplasia of the eyelid. The lack of evidence of a precancerous keratosis in the epidermal tissue immediately adjacent to the lesion coupled with the inflammatory reaction are important features in the differential diagnosis H and E stain. (*A* ×50 *B* ×305) (AFIP Acc. 853800)

anaplasia is less than in carcinoma, while the inflammatory reaction is greater Efforts to uncover the responsible etiologic factors by special staining methods and by obtaining an accurate history should be made

Keratoacanthoma.—Keratoacanthoma and molluscum sebaceum are terms that have been applied to a particular variety of idiopathic pseudoepitheliomatous hyperplasia which in previous years was often mistakenly called squamous cell carcinoma (Grinspan, Ereaux) This lesion has a predilection for the face, including the eyelids, and for the dorsum of the hands wrists and forearms. Although typically

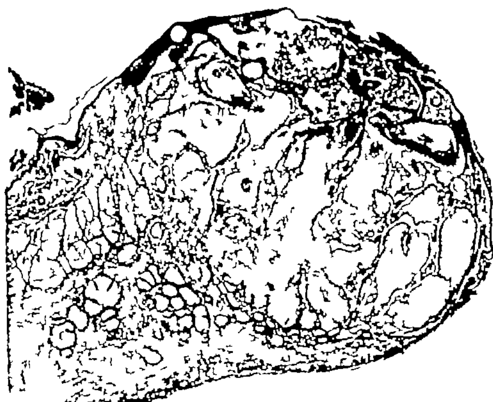


Fig 1023 —Keratoacanthoma of the lid margin The patient, a 59-year-old white man claimed the lesion developed rapidly over a two-week period It was seen as a nodular swelling with an area of necrosis on the surface Clinical diagnosis was basal cell carcinoma. H and E. stain (×15) (AFIP Acc. 819080)

affecting the "cancer age group these tumors frequently can be differentiated from carcinoma by their typical course They appear more suddenly grow rapidly and then heal spontaneously if not excised first. They also tend to present a characteristic hemispherical configuration with an umbilicated or crusted center It is because of this configuration which resembles that of molluscum contagiosum that the lesion has been called molluscum sebaceum. Microscopically keratoacanthoma is characterized by a severe degree of pseudoepitheliomatous hyperplasia which may appear frightfully similar to cancer (Fig 1023) Important features in differential diagnosis are (1) the configuration of the lesion, (2) the reticulated pattern of anastomosing bands of keratinizing epithelium in the center of the lesion, (3) the umbilicated center which may be filled in with a thick mass of keratin, and (4)

the remarkably normal appearance of the adjacent epidermis where it is pulled up over the nodule (Fig 1024) The last feature is of special importance for in true squamous cell carcinoma the adjacent skin usually shows evidence of senile keratosis.

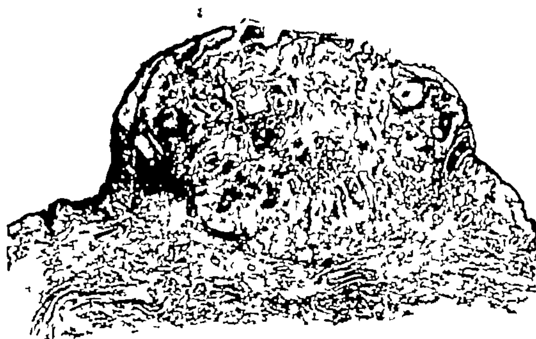




Fig 1024 —This keratoacanthoma of the eyelid excised from a 44-year-old white man, was originally interpreted as a squamous cell carcinoma. H and E stain. (*A* ×9 *B* ×115) (AFIP Acc. 784356)

Inverted Follicular Keratosis—This condition is another morphologically specific variety of pseudoepitheliomatous hyperplasia which has a distinct predilection for the face (Helwig 1954) Involvement of the eyelids is common and in such cases an erroneous diagnosis of carcinoma may lead to disfiguring or disabling treatment. The lesion usually presents as a single papillary or nodular projection from the surface. As in keratoacanthoma, an important feature is the presence of essentially normal skin about the base and margins of the lesion Its name, inverted follicular keratosis, is derived from its outstanding histopathologic characteristics. It is a keratinizing lesion which has become inverted into itself (Fig 1025) Thus it, too has a configuration similar to that of molluscum contagiosum and keratoacanthoma. It is differentiated from these by a growth pattern which typically is observed throughout the actively proliferating masses of epidermal cells that form the bulk of its mass. Squamoid cells which have become somewhat flattened are arranged concentrically to form whorllike squamous eddies (Figs. 1025 and 1026) The lesion is believed not to carry with it any danger of malignant change

Seborrheic Keratosis—Seborrheic keratosis occurs with considerable frequency on the lids. Although it ordinarily gives no difficulty in histopathologic diagnosis, its appearance may be altered markedly as a result of superimposed inflammatory changes In such cases the added stimulus to proliferation may produce bizarre cytologic features which lead to an erroneous diagnosis of carcinoma.

Senile Keratosis—Senile keratosis, though less common than other keratotic lesions of the lids is not of unusual occurrence It is the forerunner of most true squamous cell carcinomas and its presence about the edges of a lesion is helpful in deciding whether the latter is a cancer or a pseudoepitheliomatous hyperplasia. Microscopically it presents the same features on the lids as elsewhere.

Cutaneous Horn—Cutaneous horn is a term that should probably be restricted to clinical parlance for it simply indicates the presence of a conical or fingerlike mass of horny tissue projecting from the lid margin. Microscopically cutaneous horns are not always similar Many, however prove to be examples of senile keratosis and some show changes indicative of early infiltrating squamous cell carcinoma.

"*Benign Keratosis Type Uncertain*—This is a diagnosis which must frequently be used (Fig 1027) Many of the lid lesions which worry pathologists do so for two reasons (1) the fear of missing a cancer and (2) the inability to apply a specific name to it. Possibly it is because many of the lid lesions have been altered by a variety of irritants, including medications that a seemingly large proportion defy specific histopathologic diagnosis The pathologist should not hesitate using the humble diagnosis, "benign keratotic lesion."

Miscellaneous—Other proliferative lesions including such viral infections as molluscum contagiosum occur on the lids but these rarely give rise to difficulties in differential diagnosis.

Melanotic Tumors.—Melanotic tumors and related lesions include nevi malignant melanomas, precancerous and cancerous melanosis, and melanosis oculi.

Nevi.—Nevi have already been mentioned on page 982, for they are generally considered to be congenital or developmental tumors, even though their presence

may not be recognized until growth or pigmentation takes place during adolescence or later The flat junctional type is most important, for this is the lesion from which many malignant melanomas are believed to arise The histopathologic characteristics of junctional, dermal and compound nevi of the lids are no different from those of other areas (see p 113)





Fig. 1025—*A* Inverted follicular keratosis of the lid margin in a 63-year-old white man. The lesion had been present for over a year and clinically was believed to be a basal cell carcinoma. *H* and E stain (×16) (AFIP Acc 844610) *B* A portion of the same lesion is shown at greater magnification (×145) to illustrate the typical "squamous eddies."

Precancerous Melanosis—Precancerous melanosis is a condition which may involve either or both surfaces of the lid in association with the bulbar conjunctiva. It is typically a diffuse superficial nonelevated pigmented lesion involving a large surface area with ill-defined borders. It is not congenital but develops insidiously during adult life. Its course may be progressive or stationary or it may wax and



Fig. 1026—Typical squamous eddies of inverted follicular keratosis from a recurrent lesion of the eyelid, which was originally interpreted as a squamous cell carcinoma. H. and E. stain. (*A* ×115 *B* ×305) (AFIP Acc. 784875)

wane (Reese) This condition is described more fully under the heading Bulbar Conjunctiva and Cornea (p 1029), for it is in these locations that the entity is most often encountered Precancerous melanosis is of importance, as its name implies,





Fig 1027 —Benign keratosis type uncertain, was the consensus of several consultants who examined this lesion of the upper eyelid Clinically it was believed to be a verucca but the initial histopathologic diagnosis was squamous cell carcinoma. H. and E stain. (*A* ×23 *B* ×115) (AFIP Acc. 738582)

because malignant melanoma frequently supervenes. It should not be confused with melanosis oculi which is a congenital hyperpigmentation of the ocular tissues.

Malignant Melanoma—Malignant melanoma of the eyelid may originate from a nevus that has been present for many years, from a precancerous melanosis of variable duration or from what is believed to have been previously normal skin or conjunctiva. In general malignant melanomas of the lid carry a very grave prognosis for they tend to metastasize early by lymphatics and by the blood stream. This is in decided contrast with malignant melanomas of the bulbar conjunctiva (see p 1029) and of the uvea (see p 1059) which have a much more favorable prognosis. The histopathologic characteristics of malignant melanomas of the lid are comparable to those of the skin and mucous membranes elsewhere (see p 120)

Glandular and Other Adnexal Tumors.—These tumors are potentially numerous because of the variety of specialized cutaneous appendages in the lids but actually they are not common

Adenoma and Adenocarcinoma of Sebaceous Glands—Sebaceous gland adenomas and adenocarcinomas may arise from the cutaneous sebaceous glands, from the glands of Zeis or from the meibomian gland True solitary neoplasms of the cutaneous sebaceous glands are extremely rare Of importance however, are the multiple tiny hamartomatous proliferations of the sebaceous glands of the face which are among the most characteristic features of tuberous sclerosis. These frequently occur on the lids along with the more typical distribution over the malar eminences nasolabial region, and the chin.

Solitary adenomas of the meibomian and Zeis glands are rarely seen in the laboratory though they may be more common than is generally believed. The meibomian gland tumors for example may simulate a chalazion and be removed by curettage. Such curettings are rarely submitted for microscopic examination hence one does not know how often such tumors are missed In the case of malignant tumors however recurrence is likely It is for this reason that recurrent chalazia are often excised and sent to the pathology laboratory In reviewing the histories of patients with meibomian gland cancers it is impressive that the usual story is one of repeated curettages for chalazia before a neoplasm is suspected and a biopsy obtained In Straatsma's series of 16 cases, an average period of three years elapsed between onset of growth and definitive surgery and in only four cases was the definitive operation performed as a primary procedure. Following early complete excisional surgery the prognosis of meibomian gland carcinomas is good, but extension along the regional lymphatics to the preauricular submaxillary and cervical lymph nodes does occur Extension into the facial bones and distant metastasis have also been reported (Straatsma)

Microscopically adenomas of the meibomian glands reveal a proliferation of the sebaceous glands with varying degrees of organizational disturbance within the tarsus. A spectrum of changes from adenomatoid hyperplasia with fairly well preserved meibomian gland architecture (Fig 1028) to widespread replacement of the tarsus by poorly organized masses of sebaceous glands (Fig 1029) may be observed. Malignant meibomian gland tumors also show considerable histologic and cytologic variation merging with adenomas on the one hand and with very ana

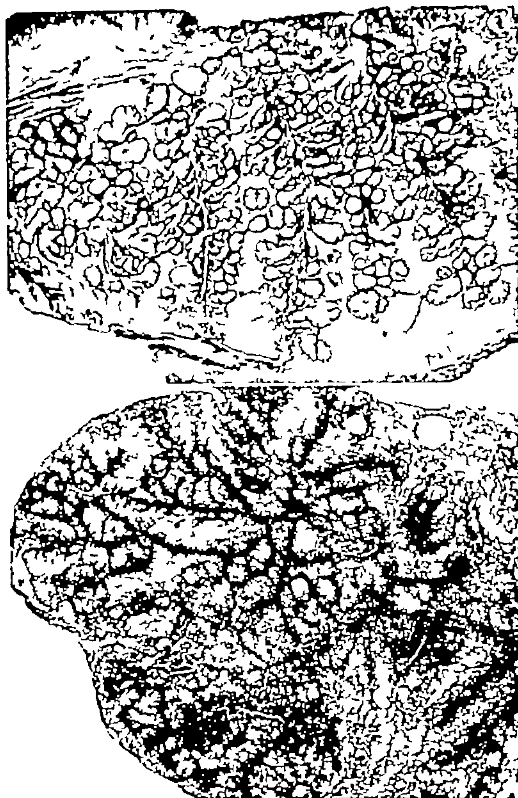


Fig 1028—Adenomatous hyperplasia and hypertrophy of the meibomian gland. H and E. stain (×22) (AFIP Acc 514703)

Fig 1029—Adenoma of the meibomian gland H and E stain (×65) (AFIP Acc. 209672.)



Fig. 1030.—Adenocarcinoma arising in the meibomian gland. Many of the tumor cells, especially those in the center of the ductlike structure, are filled with vividly stained fatty material. Oil red 0 stain. (×65.) (AFIP Acc. 541358.)

Fig. 1031.—Adenocarcinoma of the meibomian gland. Plugs of completely necrotic tumor fill the central portions of ductlike tubular masses of neoplastic tissue. H. and E. stain. (×65.) (AFIP Acc. 541358.)

plastic epithelial tumors of uncertain histogenesis on the other The former are easily recognized, first, by their position within the tarsus and their obvious anatomic relation to the meibomian gland and, second, by their cytologic characteristics In such tumors the cells continue to exhibit sebaceous differentiation (Fig 1030) which is very dramatically brought out by frozen sections stained for fat. More rapidly growing tumors may be characterized by extensive necrosis of the central areas of neoplastic lobules giving rise to a comedocarcinoma pattern (Fig 1031) Still others will exhibit sheetlike masses of poorly differentiated cells with many mitotic figures while others produce spindle-shaped tumor cells (Fig 1032) The pattern of growth of meibomian gland carcinomas varies from that of an in situ proliferation with preservation of gland architecture to massive lesions which involve the full thickness of the lid and destroy most of the normal landmarks Pagetoid involvement of the overlying skin has already been mentioned (Fig 1020)

Adenoma and Adenocarcinoma of Sweat Glands—Sweat gland adenomas and adenocarcinomas arising in either Moll's glands or the cutaneous glands are even more rare than the sebaceous gland tumors Apocrine type adenomas and adenocarcinomas do arise from the glands of Moll, and on occasion these do give rise to pagetoid extensions in the overlying skin (see p 993) Mixed tumors similar to those of the lacrimal and salivary glands (see p 425) are also found in the lids, presumably arising from the sweat glands

Calcifying Epithelioma of Malherbe—This is a hard solitary, deep-seated but usually movable tumor which Helwig and others believe to be a benign neoplasm arising from hair follicles hence its new name hair matrixoma (Helwig 1954) The tumor, which is generally covered by normal skin occurs most often on the face and upper extremities (Lever Helwig), and involvement of the eyelids is not unusual. The histopathologic characteristics of this tumor as it occurs in the lid are similar to those elsewhere in the skin (see p 106) The same great variation in cellularity mummification calcification and ossification are observed Although some are extremely cellular exhibit numerous mitotic figures and may be erroneously diagnosed as squamous cell carcinoma arising in an epithelial cyst of the lid margin truly malignant behavior is not observed

Mesenchymal Tumors.—Mesenchymal tumors, except for those of developmental origin (hamartomatous growths) such as hemangiomas and neurofibromas (see p 1039) are extremely uncommon This statement applies to benign as well as malignant neoplasms

Fibromatosis—Fibromatosis a type of reactive fibroblastic proliferation (see p 837), is rarely observed in the lid but when encountered there, it is very likely to be called a fibroma or fibrosarcoma. Actually a true fibroma or fibrosarcoma of the lid is of questionable occurrence.

Sarcomas—Sarcomas of all types are very uncommon Embryonal rhabdomyosarcomas of the orbit may involve the lids, and occasionally the tumor may seem to arise in the lid This tumor of young children is considered more fully on page 1018.

Lymphomas—Lymphomas arising in the lids are rarely a manifestation of such systemic malignant diseases as *reticulum cell sarcoma lymphosarcoma, or* Hodgkin's disease Most of the tumorlike proliferations which are encountered in

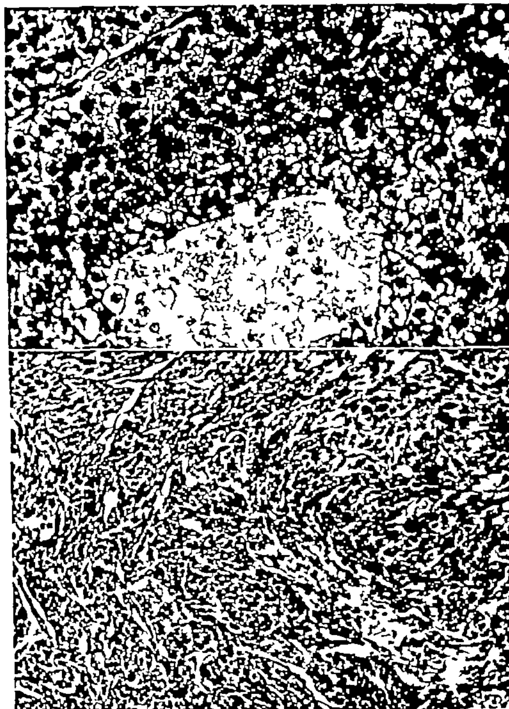


Fig. 1032.—Adenocarcinoma of the meibomian gland. *A* At the bottom of this field the tumor cells are more differentiated than are those at the top. H. and E. stain. (×305.) *B* Another field of the same tumor illustrating a tendency for the cells to become fusiform even though many still continue to produce fatty material. H. and E. stain. (×115.) (AFIP Acc. 804889.)

the lids are localized phenomena of obscure etiology Some are obviously inflammatory, for in addition to the lymphocytic proliferation, there is reticulum cell hyperplasia endothelial proliferation and plasmacytosis In other instances there is a very uniform infiltration by small or large lymphocytes, and a well-differentiated lymphocytic lymphoma can be ruled out only after a complete clinical and hematologic study with prolonged follow up investigation The occurrence of systemic involvement years after the initial appearance of a lymphoid lesion of the lids serves as a warning against dismissing the possibility of malignant lymphoma until one has had the benefit of exhaustive and prolonged clinical study

Secondary Tumors —Secondary tumors involve the lids in several ways, often giving the impression of a primary process within the lids

Palpebral Lobe of Lacrimal Gland —Lacrimal gland tumors or nonneoplastic enlargements which involve the palpebral lobe may be biopsied in the belief that they represent intrinsic lesions of the lids

Orbital Dermoids —Orbital dermoids often encroach upon the lid in such a way that they may be excised as primary cysts of the lid

Malignant Neoplasms of the Nose and Paranasal Sinuses —These neoplasms may first make their presence known as a result of their direct spread into the lids. Similarly a tumor of the nasolacrimal sac may appear as a primary lesion of the conjunctiva about the punctum.

Leukemia —Leukemia especially the acute leukemias of childhood not uncommonly involve the lids. Tumefactions of the lids, with or without hemorrhage may be the initial manifestation of the disease

Metastases From Distant Sites —Metastases of malignant tumors of distant sites to the eyelids are encountered from time to time with or without other evidence of metastatic disease in the eye or orbit

DISEASES OF LACRIMAL PASSAGES

Diseases of the lacrimal passages which are of importance to the surgical pathologist are characterized by epiphora, the imperfect drainage of tears so that they flow over the lid margin onto the cheek and by varying degrees of swelling induration and inflammation of the lower lid at its nasal end While inflammatory obstructions of these passages are common neoplastic lesions are rare.

Canaliculitis and Dacryocystitis

Canaliculitis and dacryocystitis may be the result of direct spread of inflammatory processes in such neighboring structures as the conjunctiva or nose but more often their pathogenesis is obscure Acute and chronic types are recognized and the inflammatory reaction may be suppurative granulomatous or necrotizing with the formation of fistulous tracts to the skin surface below the lid near the base of the nose. The lacrimal passages become filled with purulent exudate in the acute suppurative types while in the chronic forms the passages are narrowed by the inflammatory thickening of the walls of the lacrimal canal or sac. Frequently

there is also hyperplasia of the lining epithelium and hypersecretion of mucus. At times the degree of papillomatous or adenomatous hyperplasia of the sac may give rise to difficulties in differential diagnosis.

Inflammatory Pseudotumor

Though really a misnomer this term is often used by ophthalmologists to denote a nonneoplastic mass derived as a consequence of an inflammatory process. To be classified as a pseudotumor the lesion should have more of the clinical features of a neoplasm than of an inflammatory process. Such tumefactions are more often encountered in the orbit (see p 1015), but they may arise also in the lacrimal sac. Two types are recognized histologically and one has already been mentioned. This is the pseudoepitheliomatous hyperplasia of the mucosal lining More often however pseudotumors are composed of granulation tissue which lifts up the epithelium to form polypoid masses that fill the lumen of the sac. In some cases there may be massive lymphocytic proliferation and the question of a primary malignant lymphoma may arise Generally however, pseudotumors are readily recognized as nonneoplastic once they are seen under the microscope.

Lacrimal Mucocele

Lacrimal mucocele is another complication of chronic inflammation of the lacrimal sac. A low-grade obstructive lesion with a relatively intact and possibly hypersecreting mucosa may lead to great distention of the sac by accumulated secretions. A discrete swelling occurs just below the inner canthus between the lid and the nose. If untreated it may enlarge progressively to occupy much of the side of the face and hide the eye The contents of the cyst may be clear or milky fluid or gelatinous fibrinous or flocculent, sterile or infected (Duke Elder) Microscopically the cyst wall reveals varying degrees of atrophy degeneration, hyperplasia and hypersecretion of the mucosa, and chronic inflammation of the subepithelial tissues.

Dacryolithiasis

Dacryolithiasis and concretions in the lacrimal canaliculus are of uncertain pathogenesis, but they are generally believed to be the result of a low-grade inflammatory process Mycotic infections are believed by some authorities to account for most tear stones." If such concretions are crushed and examined microscopically they will be seen to contain myriad mycelial elements imbedded in a relatively acellular matrix. Others, however are laminated mineralized stones without recognizable fungal or bacterial forms.

Neoplasms

Neoplasms of the lacrimal passages are rare Papillomas similar to those arising in the conjunctiva of the lid (see p 993) may form in the punctum, within the canaliculus, or in the sac Inflammatory pseudoepitheliomatous hyperplasia, however is seen more often Frequently it is impossible to decide whether in a given case a papilloma obstructed the passages and led to secondary inflammatory

reaction or whether a primary inflammatory process stimulated the epithelial hyperplasia.

From the clinical point of view it is usually not possible to differentiate malignant tumors of the lacrimal passages from benign neoplasms and pseudotumors. At first when the lesions are still small they obstruct the passages and give rise to epiphora and a low grade inflammatory reaction. Later they produce obvious tumefaction. One or more attempts to open up the passages by probing or by surgical drainage are made before material is obtained for microscopic study. All malignant tumors of the lacrimal passages except for carcinoma are exceedingly rare and even carcinoma is distinctly uncommon. These tumors are usually moderately well-differentiated squamous carcinomas similar in appearance to those arising from the mucosa of the nose or in the conjunctiva. They tend to form papillary projections into the lumen and spread along natural surfaces but they also infiltrate directly into adjacent tissues.

DISEASES OF THE LACRIMAL GLAND

Diseases of the lacrimal gland rarely come to the attention of pathologists, for it is usually only when a neoplasm cannot be excluded or when disfiguring enlargement occurs that the gland or a portion of it is excised. Biopsies of the lacrimal gland are also made to assist in the differential diagnosis of Mikulicz's and Sjögren's syndromes.

Dacryoadenitis

Dacryoadenitis of the acute type is rare and of no importance to us here. Chronic varieties include specific and nonspecific inflammatory processes. When in addition to enlargement of both lacrimal glands there is also parotid or other salivary gland enlargement the condition is known as *Mikulicz's syndrome*. This may be the result of a variety of specific diseases including sarcoidosis, tuberculosis, syphilis, mumps, Graves' disease, lymphoma, and leukemia (Duke Elder).

More often, however, neither clinical nor histopathologic studies lead to a specific diagnosis, and in such cases the diagnosis of *Mikulicz's disease* may be justified. Typically it begins with insidious but progressive enlargement of one lacrimal gland. Subsequently, after a period of months or years, the other lacrimal and the salivary glands become involved, often symmetrically. Even the accessory lacrimal glands of the conjunctiva and the minor salivary glands may participate. Histopathologic study does not reveal a pathognomonic picture, but usually there is pronounced lymphoid and reticulum cell hyperplasia. When the latter is pronounced and when discrete epithelioid tubercles are numerous, the possibility of sarcoidosis must be considered. Other leukocytic types, including eosinophils, may be prominent. The inflammatory elements infiltrate the gland diffusely, often leading to widespread atrophy of the acinar elements. In advanced cases it may be difficult to recognize the tissue as glandular, for only occasional ducts remain. Because of the numerous clinicopathologic variations that are encountered and because a specific etiology has never been established, the tendency to question Mikulicz's disease as a nosologic entity has grown (Duke Elder).

Unilateral enlargement of the lacrimal gland with or without associated salivary gland involvement may be observed in the same group of diseases which may give rise to Mikulicz's syndrome. Chronic dacryoadenitis with unilateral or bilateral enlargement may also arise as a complication of other primary ocular disease such as trachoma.

Atrophy: Sjögren's Syndrome

Sjögren's syndrome is characterized by a failure of lacrimal secretion and consequent keratoconjunctivitis sicca, usually in postmenopausal women. Typically there is evidence of a systemic disorder affecting mucous membranes and their associated glands. It is believed that degeneration of the secretory portions of the lacrimal and salivary glands is the essential feature of the pathologic anatomy in Sjögren's syndrome, though such secondary changes as lymphocytic infiltration, fibrosis, and hyalinization are commonly present. Were it not for the diffuse involvement of the entire conjunctiva and the accessory lacrimal glands, the serious corneal degeneration would probably not occur, for surgical removal of the lacrimal glands rarely gives rise to a clinicopathologic picture of keratoconjunctivitis sicca (Duke-Elder). Superinfection is common.

Cysts

Cysts are rare causes of enlargement of the lacrimal gland. A simple retention cyst of the palpebral lobe is the type most often encountered.

Neoplasms

Neoplasms of the lacrimal gland are of considerable importance, not only because they account for most of the surgical procedures performed on these glands, but also because all too frequently they are not treated adequately by ophthalmic surgeons. Most of these neoplasms arise in the orbital lobe where the gland is firmly attached to the orbital rim about the lacrimal fossa. The bone tends to restrict growth in its direction; hence the enlarging tumor characteristically displaces the eye downward and inward. This frequently leads to diplopia. Other visual changes produced by pressure on the optic nerve, alteration in the contour of the globe, or corneal damage are seldom observed. The much rarer lacrimal gland tumors arising in the palpebral lobe produce tumefaction of the outer portion of the upper lid over the external canthus. The lid is projected forward, upward, and outward. Subconjunctival extension past the fornix onto the bulbar conjunctiva may be observed. Thus these rare neoplasms of the palpebral lobe are often mistaken clinically for other types of lid and epibulbar tumors.

The histopathologic characteristics of lacrimal gland tumors are similar to those of the salivary glands (see page 425). Mixed tumors are by far the most frequent, accounting for 75 to 90 per cent of the reported cases. In a recent (unpublished) review of 80 epithelial tumors of the lacrimal gland on file in the Registry of Ophthalmic Pathology I found one half to be benign mixed tumors. One third of the remainder were considered malignant mixed tumors and the rest

were carcinomas unrelated to mixed tumors Among the latter adenoid cystic carcinomas were most numerous

Typically the mixed tumor produces an insidious enlargement of the orbital portion of the lacrimal gland during middle adult life We have, however, seen cases in children and in the elderly As the tumor grows, pseudoencapsulation occurs as a result of compression of adjacent tissues Actually, however, the tumor frequently infiltrates this pseudocapsule If as is frequently done, the surgeon tries to shell out the neoplasm from its capsule he actually leaves behind many minute extensions of the tumor within the capsule This is one reason for the high recurrence rate after "excisions of lacrimal gland tumors Another even more serious difficulty arises as a result of the position of these tumors in the lacrimal fossa. Here there is less opportunity for a soft tissue pseudocapsule to form about the enlarging mass. The neoplasm becomes adherent to the periosteum and may actually infiltrate the bone. For this reason some surgeons advocate excision of that part of the orbital rim without trying to dissect the gland out of the lacrimal fossa

Because so many of these lacrimal gland tumors have not been completely and adequately removed at the initial operation there has been an excessively high recurrence rate (Sanders) It is even more difficult to treat the recurrences, for these are often multiple The carcinomas have a very poor prognosis.

In addition to the epithelial tumors of the lacrimal gland enlargement, but more often lymphoid hyperplasia in these glands is unrelated to generalized diseases of the reticuloendothelial system. In the course of leukemia or one of the malignant lymphomas, the lacrimal glands may become involved along with other tissues, but rarely do such cases come to the attention of surgical pathologists.

NEOPLASMS AND OTHER TUMEFACTIONS OF THE ORBIT

Neoplasms and other tumefactions of the orbit are logically considered together from the viewpoint of the surgeon and surgical pathologist. Other orbital diseases that do not involve the differential diagnosis of neoplasms rarely come to the pathologist's attention. It is extremely difficult to state categorically the relative frequency of the numerous lesions which we must consider here The nature of one's material as well as the patient's age and general state of health must always be kept in mind. Furthermore many of the lesions which we must consider here actually begin in adjacent structures and involve the orbit only secondarily A few examples that will make this point clear may be cited. To the radiologist one of the most common orbital lesions producing displacement of the eye, and one which must therefore be considered in the differential diagnosis of orbital neoplasms, is a mucocele arising in one of the paranasal sinuses (Pfeiffer)

Hemangiomas which most ophthalmologists and ophthalmic pathologists believe to be the commonest of orbital tumors are ranked fourth behind mucoceles, meningiomas, and craniostenosis by the radiologist Pfeiffer

If one should ask a pediatrician or a general pathologist in a children's hospital "What is the malignant tumor you see most frequently in the orbit? the answer would be "metastatic neuroblastoma Yet those of us who deal mainly with surgical material submitted to the laboratory by ophthalmic surgeons rarely see

these orbital metastases of neuroblastomas. Much more frequent in our experience is the primary embryonal type of rhabdomyosarcoma.

Congenital and Developmental Conditions

Congenital and developmental lesions account for a large number of orbital tumor cases, for although the specific types of tumors which fall into this category are few, they include some of the most frequent, especially in the younger age group

Angioma.—Angiomas are generally considered to be the most common of all orbital tumors that require surgical treatment. These are generally of blood vessel origin, for lymphangiomas of the orbit are comparatively rare. Although encountered in any age group angiomatous tumors typically make their presence known early in life. In Ingalls series angiomas accounted for one fourth of the orbital tumors removed during the first decade but an equal number of these tumors were obtained from patients over 40 years of age. All types of angiomas may be observed but the cavernous is the commonest (Fig 1033) These tumors rarely present difficulties in histopathologic diagnosis for they are not significantly dissimilar from angiomas of other regions. Sclerosing hemangiomas are rare in the orbit but when encountered they may be misinterpreted as a primary sarcoma.

Neurofibroma.—Neurofibromas are also basically hamartomatous lesions, but they are much less common in the orbit than are the vascular tumors. These orbital tumors may be merely one of a number of manifestations of Recklinghausen's disease, but on occasion they are also encountered as isolated lesions. In the former situation there may be gross deformity of the orbit and lids as well as diffuse involvement of the orbital nerves, while in the latter the tumor is more likely to be localized, though not encapsulated like the neurilemoma.

Dermoid and Related Cysts.—Dermoid cysts are among the most common of orbital tumors, especially during the first decade Typically they occur in the upper temporal part of the orbit anteriorly and therefore encroach upon the lid and brow They may also arise within the orbital bones, especially the frontal producing sharply demarcated defects which are very typical roentgenographically (Pfeiffer) These cysts are generally believed to develop as a result of inclusions of surface ectoderm and they do not represent true teratomas They are lined by cutaneous tissue containing all of the usual skin appendages. The cyst lumen is filled with desquamated keratin and secretions from the cutaneous glands. Other elements found in teratoid lesions (e.g neural tissues) are absent. True teratomas of the orbit are very rare.

Dermoid cysts may or may not be noticed during the first few years of life, and growth may be delayed until puberty or later Sometimes as a result of trauma the contents of the cyst are discharged. This usually gives rise to a severe chronic inflammatory reaction which may obscure the original lesion A foreign body type of granuloma in the upper temporal quadrant of the orbit should therefore lead one to suspect the possibility of a ruptured dermoid cyst. A variation of the dermoid cyst has been called a cholesteatoma, but this term is confusing as it has also been used to designate another lesion which has different histopathologic charac

teristics. Most writers have applied the term to a variety of epidermoid inclusion cysts in which the lumen is replaced by a ball of dense hyalinized keratin which macroscopically resembles a pearl (hence the synonym, pearl cyst) Other authors (see Ingalls) have applied the term to granulomatous lesions containing great numbers of cholesterol clefts and a predominance of macrophages and giant cells possessing abundant foamy cytoplasm Such lesions usually have no definite cystic structure, and although some could be derived from traumatized dermoid cysts, it is likely that others are secondary to hemorrhage or infection



Fig. 1033 —Huge hemangioma of the orbit. H and E stain (×2) (AFIP Acc. 829429)

Mucocele.—Mucoceles of the frontal and ethmoid sinuses are relatively common lesions of great clinical importance in the differential diagnosis of orbital tumors. Generally of insidious onset and characterized by very slow symptomless enlargement mucoceles often erode the sinus walls and produce characteristic radiologic defects (Pfeiffer 1943) Typically the eye is displaced downward and temporally Histopathologic diagnosis is easy, provided one is aware of the possibility of sinus mucoceles in the orbit. The orbital mass is cystic and is lined by mucus-secreting sinus mucosa which shows various changes incident to the long standing chronic inflammatory process.

Systemic Diseases

Systemic diseases which produce orbital lesions of interest to surgical pathologists are very few. Only three groups need be considered here.

Endocrinopathic Exophthalmos.—*Thyrotoxic exophthalmos* (exophthalmic goiter, Graves' disease) and *thyrotropic exophthalmos* (exophthalmic ophthalmoplegia) are well known causes of bilateral orbital pathology, but rarely does biopsy material from such cases come to the attention of the surgical pathologist. Even



Fig. 1034.—*A*, A 65-year-old white woman who had had malignant exophthalmos of about ten months' duration finally died of congestive heart failure. *B*, At autopsy the extraocular muscles were found to be massively thickened (Fig. 1035). (AFIP Acc. 692463.)

in those cases of Graves' disease with unilateral exophthalmos clinical diagnosis is relatively easy and there are no indications for orbital exploration. On the other hand, unilateral exophthalmic ophthalmoplegia may well be mistaken for a primary orbital neoplasm, and a number of eyes have been sacrificed because of this confusion (Duke-Elder). Unilateral orbital involvement occurs with sufficient frequency in both forms of endocrine exophthalmos so that these conditions should always be considered in the differential diagnosis of orbital tumors.

Histopathologic changes observed in the severe cases which are most likely to come to the attention of surgical pathologists include widespread edema and chronic inflammation of all the orbital tissues. The most striking gross alterations are observed in the extraocular muscles which may be massively enlarged (Fig. 1034). Muscle fibers degenerate and become hyalinized. A great increase in the interstitial connective tissue, including both cellular elements and ground substance, is observed particularly in the muscles (Fig. 1035) but also in the other orbital tissues.

Hand-Schüller-Christian Syndrome.—This syndrome has as one of its outstanding clinical features the occurrence of proptosis produced by granulomatous lesions in the orbital bones. Once considered a primary metabolic disorder involving fat metabolism by the reticuloendothelial system, the disease is now generally believed to be a chronic *form of disseminated histiocytosis* related to Letterer-Siwe's disease and to eosinophilic granuloma of bone (see p. 774). Orbital lesions are less commonly found in Letterer-Siwe's disease and eosinophilic granuloma, though they do occur (Fig. 1036).

Wegener's Granulomatosis.—Wegener's granulomatosis has recently been reported (Straatsma, 1957) to involve the eyes and/or orbits in almost half the cases. The disease is a systemic disorder, usually fatal, of unknown etiology, characterized anatomically by the production of necrotizing granulomatous lesions in the respiratory tract, diffuse arteritis and focal glomerulonephritis. Orbital involvement which results in exophthalmos occurs as a complication of lesions in the upper respiratory tract. Extensive necrosis and leukocytic infiltration of the optic nerve and intraocular tissues may also be observed.

Inflammatory Processes

Inflammatory processes which involve the orbit cover a broad spectrum, for the orbit may become secondarily inflamed by lesions of diverse etiology beginning in the face, eyes, nose, sinuses, orbital bones, blood vessels, brain and meninges. Generally it is only when such inflammations simulate neoplasms that orbital exploration is undertaken and tissue is obtained for histopathologic diagnosis. Based upon their microscopic features, these inflammatory masses fall into two main categories.

Specific Granulomas.—Specific granulomas including those of tuberculosis and sarcoidosis are rare.

Nonspecific "Pseudotumors."—Nonspecific chronic inflammations ("pseudotumors" of orbit) are very much more frequent than are the specific infectious granulomas. In fact, they vie with dermoid cysts and lymphomas for second place (after hemangiomas) as causes of space-occupying orbital masses. Such lesions clinically may simulate a neoplasm so closely that until recent years they frequently were treated by radical surgery (Reese, 1951), hence the popular name of "pseudotumor" was applied to these lesions by ophthalmologists.

Undoubtedly these pseudotumors represent an etiologically and pathogenically heterogeneous group. *The pathologic features which they share include* (1) the formation of an indurated orbital mass often surrounding the optic nerve and in



Fig 1035 —Varying degrees of replacement of skeletal muscle fibers by fibrous connective tissue, ground substance, and chronic inflammatory cells are observed in the massively thickened extraocular muscles of the patient illustrated in Fig 1034 (×145)

Fig 1036 —Orbital involvement in a fatal case of Letterer-Siwe s disease The bony walls of the optic foramen are partially destroyed by the granulomatous inflammatory tissue The intracanalicular portion of the optic nerve is seen in the center of the field. H. and E. stain. (×11) (AFIP Acc 795765) (Courtesy Dr John T Elston)



Fig 1037 —"Pseudotumor" of orbit The optic nerve and other orbital tissues are "frozen" in a dense mass of nonspecific chronic inflammatory tissue H and E stain. (×5½) (AFIP Acc. 33691)

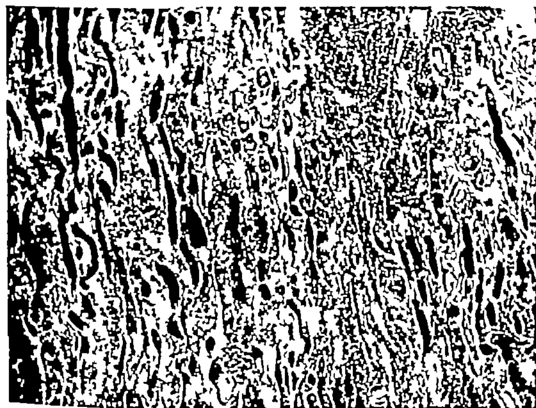


Fig. 1038 —Edema and lymphocytic infiltration of the extraocular muscles observed in this case of orbital "pseudotumor" suggest the possibility of unilateral endocrinopathic exophthalmos. H. and E. stain (×115) (AFIP Acc. 859063)

corporating one or more of the extraocular muscles (2) a tissue reaction which includes exudation of fluid excessive production of ground substance the mobilization of chronic inflammatory cells, vascular proliferation and hyperplasia of connective tissues and (3) the absence of demonstrable etiologic agents or of otherwise diagnostic histopathologic alterations indicative of such specific disease entities as Hodgkin's disease cranial arteritis etc. (Fig 1037) This is not to say however, that the microscopic features are uniform from case to case quite the contrary! In some instances the proliferation of blood vessels and ground substance resembles that of exuberant granulation tissue. At times the lymphoid hyperplasia with follicle formation is of such intensity that the picture resembles that which is characteristic of orbital lymphomas (see p 1018) Other cases with prominent involvement of extraocular muscles suggest the possibility of thyrotropic exophthalmos (Fig 1038) A well-developed granulomatous reaction about small pools of fat is observed in certain cases such lesions may suggest traumatic fat necrosis. Others containing large numbers of cholesterol clefts and many foamy macrophages and giant cells suggest an area of old suppuration or hemorrhage. Periphlebitis is prominent in certain cases and some of these may present a significant eosinophilia suggesting the possibility of a hypersensitivity angiitis. Rarely the picture merges with that of sclerosing hemangioma or fasciitis.

Primary Neoplasms

Primary neoplasms which are truly malignant are extremely rare in the orbit, notwithstanding the fact that this area contains so many tissues capable of neoplasia.

Connective Tissue Tumors.—Connective tissue tumors of the orbit, both benign and malignant, are extremely rare. Only the undifferentiated or botryoid type of rhabdomyosarcoma is encountered with any degree of regularity In the author's experience this is the most frequently observed malignant tumor of the orbit in children Microscopically it resembles the undifferentiated rhabdomyosarcomas of childhood seen in other anatomical locations (see p 858) Typical strap cells and fibers containing well-differentiated cross striations usually are inconspicuous. It has been only during recent years that the relative frequency of this tumor in the orbit has been recognized. Formerly such neoplasms were misdiagnosed as neuroblastomas, fibrosarcomas, myxosarcomas, etc.

Fibromas lipomas, osteomas and their malignant counterparts have all been reported but they are of little importance. One possible exception to this statement concerns the occurrence of osteogenic and other sarcomas arising in the orbital tissues as a late complication of extensive radiation therapy Several cases have already been reported (Zimmerman) As the number of children who have survived extensive radiation therapy for retinoblastoma, glioma, and other lesions increases, we may anticipate seeing more cases of postirradiation sarcoma of the orbit.

Lymphoid Tumors.—Lymphoid tumors of the orbit present great difficulties in histopathologic diagnoses. Such lesions may develop in the course of a previously recognized lymphosarcoma or reticulum cell sarcoma, but much more often

the lymphoid tumor of the orbit lacrimal gland, or conjunctiva is not accompa by any clinical or hematologic evidence of a systemic disease Microscopi the cases fall into three main groups The smallest but most important cont those lesions which are quite obviously malignant neoplasms Of these, the jority are reticulum cell sarcoma and the next in frequency is the lymphosarc Follicular lymphoma and Hodgkin's disease are distinctly rare The two la groups of lymphoid tumors include (1) those which are fairly obvious example severe reactive hyperplasia and (2) those which are characterized by a rather form but widespread proliferation of lymphocytes In the former one freque observes considerable pleomorphism a variety of cell types participating vasc proliferation and prominent follicles with reactive centers It is the latter gr characterized by a monotonous lymphocytic proliferation frequently with appa infiltration of orbital fat, blood vessels, and nerves which presents most of exceedingly difficult problems in differential diagnosis. At present we believe such lymphocytomas are benign for they generally respond to very small dose radiation, are not associated with other evidence of systemic disease and do recur or metastasize following therapy It is possible, however that much lo periods of follow-up will be required to properly ascertain the behavior of t lesions.

Glioma of the Optic Nerve.—Gliomas of the optic nerve are relatively slow-growing tumors which usually arise within the orbital segment of the ne The optic nerve is not a true peripheral nerve but in reality is a fiber tract of central nervous system It contains no Schwann cells but it does possess ol dendrocytes and astrocytes It is these interstitial cells which give rise to neoplasms which, because they have not been satisfactorily subclassified are sim called "gliomas. Considerable cytologic variation is observed among the glio not only from case to case but also in different portions of a given tumor Var degrees of cellularity are observed but generally these neoplasms are character by a low order of anaplasia This is especially true about the margins of the tu where it is often impossible to be certain where reactive gliosis ends and neopl begins. Typically there are areas of intense mucinous degeneration within tumor Frequently in such areas the tumor cells appear to be virtually lost in abundant hyaluronidase-sensitive mucoid accumulations.

As these gliomas increase in size they tend to form a bulbous enlargemen the nerve (Fig 1039) They also extend along the nerve peripherally toward eye and centrally toward the brain. In so doing they often produce great enla ment of the optic canal an important diagnostic sign for the radiologist. In s cases the optic nerve fibers are likely to be completely destroyed and the o disc typically presents the ophthalmoscopic characteristics of primary optic atro The less common tumors arising close to the globe may cause papilledema or t may actually infiltrate the nerve head. Less often the tumor first makes itself dent by intracranial extension and chiasmal involvement

Another typical growth pattern exhibited by a majority of optic nerve glio is for infiltration to take place through the pia. This leads to great thickening the arachnoid (Fig 1040) Partly this is the result of more exuberant growth

the tumor cells once they have reached the arachnoid, but equally important is the reactive proliferation of arachnoidal cells. At times this has created difficulties in differential diagnosis between glioma and meningioma. Although massive arachnoidal infiltration is very typical of these tumors rarely does extension occur through the dura. Infiltration of the orbital tissues is virtually unknown even when there is good reason to believe excision of the uninvolved optic nerve has

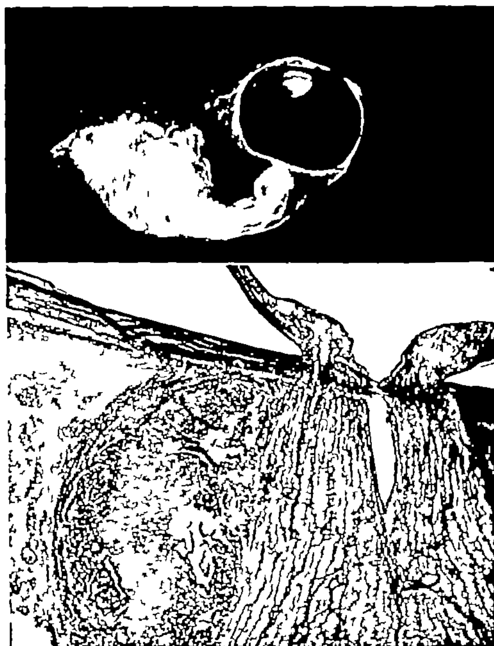


Fig. 1039.—This glioma has produced massive enlargement of the orbital segment of the optic nerve. The tumor has completely effaced the characteristic architectural features of the nerve and its meninges. (AFIP Acc 842777.)

Fig 1040.—A section through the optic nerve just anterior to the main mass of this glioma reveals minimal alteration of the parenchyma of the nerve but the meninges are greatly thickened. A combination of infiltrating tumor and arachnoidal proliferation is responsible for this meningeal thickening. H and E. stain (×20.) (AFIP Acc. 65035.)

been incomplete In such cases, however intracranial extension may take place slowly over a period of many years Metastasis does not occur via the blood stream

Secondary changes occurring within the primary tumor include in addition to the already mentioned mucoid degeneration, two others formation of cytoid bodies and ischemic necrosis (Verhoeff) The former are homogeneously eosinophilic ovoid bodies of uncertain nature which may be mistaken for ganglion cells. They resemble closely the greatly swollen degenerating nerve fibers observed in the superficial retinal exudates known as cotton wool spots. Ischemic infarcts develop as a consequence of obliteration of the vascular supply to the tumor Occasionally the degree of necrosis is such that viable neoplastic cells may be difficult to demonstrate and the diagnosis of glioma may be difficult to establish (Fig 1041)



Fig 1041 —The extensive necrosis observed within the enlarged nerve and thickened meninges in this glioma gave rise to much difficulty in histopathologic diagnosis (AFIP Acc. 703858)

Optic nerve gliomas typically make their presence known during the first decade of life. According to Davis there is a distinct association of these optic nerve tumors and Recklinghausen s disease In such cases the affected patient generally presents only minor peripheral features of the disease but bilaterality of the optic nerve involvement is more likely than in cases with no evidence of Recklinghausen s disease

Meningioma.—Meningiomas of the orbit may arise from the meninges of the optic nerve (Fig 1042) but more often they represent orbital extension of sphenoidal ridge meningiomas In many cases it is impossible to establish with certainty the site of origin of these slowly progressive neoplasms In general however the site of origin and the position of the main tumor mass account for differences in the resultant clinical picture (Reese) Those tumors arising from the orbital meninges generally produce some visual loss optic atrophy and exophthalmos. Meningiomas arising from the inner portion of the sphenoidal ridge produce more severe compression of the optic nerve within the optic canal resulting in papilledema or optic atrophy before proptosis. Those arising from the middle and outer thirds of the ridge tend to spare the optic nerve though the associated hyperostosis frequently leads to proptosis or formation of a mass in the temporal area.

Microscopically meningiomas presenting in the orbit display most of the variations encountered intracranially (see p 960) Difficulties in histopathologic diagnosis arise mainly as a result of failure to suspect the possibility of meningioma in this location, particularly when the tumor is of the fibroblastic or vascular type. These tumors grow slowly in an expansile and infiltrative manner They will infiltrate through the dura into the orbital tissue, through the pia into the parenchyma of the optic nerve, or even into the retina and choroid.

Orbital meningiomas have been reported in children but they are much more often encountered in adults.



Fig 1042.—Meningioma of the optic nerve. The meninges are greatly thickened and the optic nerve reveals severe compression atrophy H. and E stain. (×21) (AFIP Acc. 55939)

Secondary Neoplasms

Secondary tumors involving the orbit are most often extensions from primary lesions in adjacent tissues, but blood-borne metastases are also observed

Direct Spread From Adjacent Structures.—Direct spread into the orbit from primary neoplasms of adjacent structures may represent late complications of previously recognized and ineffectually treated tumors of the skin, nose, sinuses, lacrimal gland or intraocular tissues. More important diagnostically and therapeutically are those cases in which an unsuspected primary neoplasm makes itself evident first by its appearance in the orbit. Included in this category are certain retinoblastomas and malignant melanomas of the uvea which are first recognized when the eye becomes displaced by their orbital extensions. Carcinomas of the

nose and paranasal sinuses also may fail to produce diagnostic symptoms until orbital extension has occurred Another example, already considered is the meningioma which most often represents an orbital extension from an intracranial primary site.

Metastases From Distant Primary Neoplasms.—Hematogenous metastases to the orbit may on occasion be seen with many different tumors but rarely are these initial manifestations of a cancer Even the neuroblastoma which has a notorious reputation for its orbital metastases rarely does so before other diagnostic signs appear For this reason the surgical pathologist is seldom confronted with the difficult task of having to make the diagnosis of metastatic neuroblastoma Most important in this regard is the distinct possibility that a primary embryonal rhabdomyosarcoma might be misinterpreted as a metastatic tumor Another important possibility to be considered when an undifferentiated "round cell sarcoma is found in a child's orbital tissues is acute leukemia. Such orbital lesions may make their appearance before peripheral blood studies are diagnostic, but bone marrow aspirates will usually furnish a conclusive answer In the case of adults an orbital metastasis may on rare occasions be the initial manifestation of carcinoma of the breast bronchus or kidney

DISEASES OF BULBAR CONJUNCTIVA AND CORNEA

Diseases of the bulbar conjunctiva and cornea which require surgical management are not numerous.

Congenital and Developmental Lesions

The congenital and developmental lesions of importance here are dermoid tumors" and nevi.

Dermoid Tumors of Limbus.—Dermoid tumors of the bulbar conjunctiva are firm, localized, elevated opaque masses which typically occur at the limbus often encroaching upon the cornea. These are solid choristomatous masses, not to be confused with dermoid cysts of the orbit. Over the lesion the surface epithelium and the subepithelial connective tissue present the histologic features characteristic of epidermis and dermis, respectively (Fig 1043) Typically a few hairs project from the tumor The bulk of the mass is composed of thick bundles of collagen and masses of adult fat In some lesions, skin appendages are few and adipose tissue is abundant. These are called dermolipomas. Dermoid tumors of the conjunctiva are generally removed for cosmetic reasons, but those which encroach significantly upon the cornea may also give rise to visual disturbances.

Nevi.—Nevi of the bulbar conjunctiva, like those of the skin, may be observed from birth or they may become noticeable at any time during childhood, adolescence, or later At times a nevus known to have been present since infancy appears to become much larger and more pigmented at puberty Characteristically conjunctival nevi are discrete elevated lesions located on the globe in the interpalpebral zone near the limbus but they vary greatly in size shape and position. They also exhibit much variation in degree of pigmentation about a third being essentially amelanotic (Reese) Microscopically conjunctival nevi are almost al

ways of the junctional (Fig 1044) or compound varieties counterparts of the common dermal nevus of the skin are rarely observed. Frequently there are numerous solid and cystic inclusions of conjunctival epithelium intimately incorporated into the subepithelial component of these nevi. At times the epithelial inclusions may so dominate the clinical and histopathologic picture (Fig 1045) that the nevoid nature of the lesion is overlooked Varying degrees of inflammatory reaction may be present. This, too may lead to errors in clinical and pathologic diagnosis, especially in the case of nonpigmented nevi. Conjunctival nevi are excised for cosmetic reasons and because they do give rise to malignant melanoma (see p 1029)

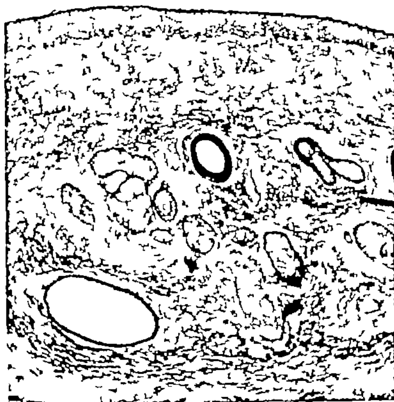


Fig. 1043 —Dermoid of the limbus. The limbal tissues resemble skin and even contain such cutaneous appendages as hair follicles, serous and sebaceous glands, adipose tissue etc. H and E. stain. (×75) (AFIP Acc. 203027) (From Friedenwald J., et al. Ophthalmic Pathology An Atlas and Textbook, Philadelphia, 1952 W B Saunders Co)

Inflammations

Inflammatory lesions of the conjunctiva do not often give rise to the type of diagnostic or therapeutic problem which requires excision and histopathologic study

Vernal Conjunctivitis.—Vernal conjunctivitis typically affects the tarsal conjunctiva (see p 987) but there is also a limbal form ay give rise to inflammatory masses requiring excision Microscopic e reveals proliferation of subepithelial connective rying degrees itheliomatous hyperplasia of the conjunctiva, ι ic inflammat rate which includes



Fig. 1044 —Junctional nevus of bulbar conjunctiva. H and E stain (×305) (AFIP Acc. 819328)

Fig. 1045 —Conjunctival nevus with many associated cystic epithelial inclusions The small round cells about the large cysts are not inflammatory cells but nevus cells. This epibulbar lesion may be analagous to hairy dermal nevi of the skin H and E stain. (×48) (AFIP Acc. 713602)

a large number of eosinophils. Vernal conjunctivitis may also be observed in association with a conjunctival nevus, in which case great confusion in clinical and pathologic diagnosis is often experienced.

Trachoma.—Trachoma and other specific viral diseases of the conjunctiva may produce great lymphoid hyperplasia with follicle formation. In the early stages these cannot be differentiated. Later trachoma tends to produce more necrosis, scarring and papillary hyperplasia. The presence of many macrophages containing particles of tissue debris (Leber cells) is said to be particularly characteristic of the lymphoid follicles of trachoma.

Granuloma Pyogenicum.—Granuloma pyogenicum and other nonspecific focalized inflammatory lesions may occasionally be excised from the bulbar conjunctiva.

Degeneration

Degenerative conditions of the bulbar conjunctiva and cornea account for many of the conjunctival lesions submitted for histopathologic study. They are encountered more frequently in persons especially exposed to the weather



Fig. 1046.—Pinguecula. There is a limbal nodule formed mainly as a result of severe senile elastosis of the subepithelial connective tissue. The overlying epithelium is atrophic. H and E. stain. (×120.) (AFIP Acc. 61823.) (From Friedenwald, J., et al. Ophthalmic Pathology: An Atlas and Textbook, Philadelphia 1952, W. B. Saunders Co.)

Pinguecula.—Pinguecula is a very common degenerative process affecting primarily the subepithelial connective tissues of the bulbar conjunctiva in the interpalpebral region. This gives rise to an elevated yellowish lesion over which the epithelium may become atrophic or thickened. Histologically the most characteristic feature is senile elastosis affecting a bandlike zone beneath the epithelium (Fig. 1046). Secondary hyalinization and calcareous degeneration may also be observed. Typically the epithelium over pingueculae becomes atrophic but at times it becomes so acanthotic and dyskeratotic that the erroneous diagnosis of carcinoma may be made (Fig. 1047).

Pterygium.—Pterygium extends into the cornea and is therefore a more important lesion than the pinguecula. Histopathologically the basic process appears to be smaller as extensive senile elastosis accounts for most of the elevation. Sec

ondary connective tissue and epithelial alterations are also observed Microscopically the pterygium can be differentiated from a pinguecula only if the advancing apical margin of the lesion in the cornea is included in the section.

Epidermidalization —Epidermidalization refers to a metaplastic thickening of the bulbar conjunctiva and limbus so that the surface epithelium resembles epidermis. The acanthosis and keratinization converts the normally transparent conjunctival epithelium into an opaque area Lesions of this type are clinically important because they give rise to problems in the differential diagnosis of leukoplakia and carcinoma.

Leukoplakia.—Leukoplakia is a clinical term indicating the presence of a white opaque plaque of thickened conjunctiva (Fig 1048) Histologically it may reveal any of a series of alterations ranging from epidermidalization on the one hand to squamous carcinoma on the other



Fig 1047 —Pinguecula. In this case there is an associated inflammatory reaction and intense pseudoepitheliomatous hyperplasia of the overlying epithelium. H. and E. stain (×75) (AFIP Acc. 710769)

Neoplasms and Related Lesions

Neoplasms, like the related lesions of importance just described also occur mainly on that part of the conjunctiva adjacent to the limbus corresponding to the palpebral fissure. Papillomas, carcinoma in situ, squamous cell carcinoma, and malignant melanoma are the principal lesions to be considered

Papillomas.—Papillomas may be sessile or fungating Often a rather broad area of involvement is observed and the lesion extends onto the cornea. Van

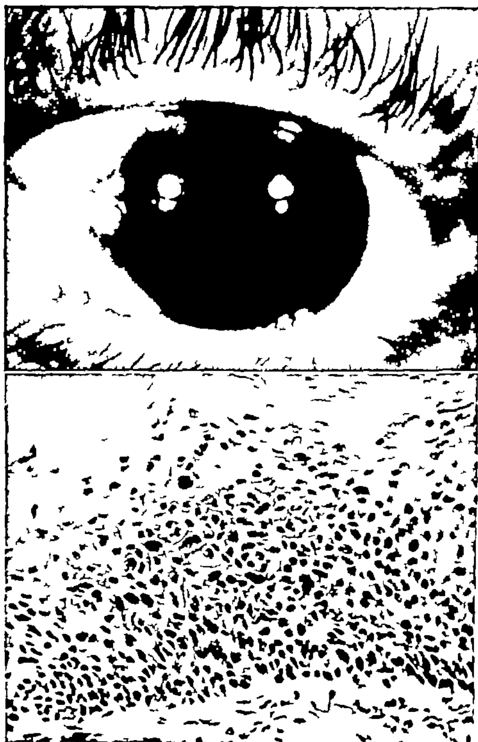


Fig. 1048.—*A* Leukoplakia. There is an opaque white plaque at the limbus in the interpalpebral area on the nasal side. This was removed by simple excision. *B* The acanthotic epithelium reveals rather marked cellularity pleomorphism, hyperchromatism, and loss of polarity H. and E stain. (×305) (AFIP Acc. 824113) (Courtesy Dr G V Simpson.)

able pigmentation occurs in papillomas of dark-skinned persons, and the lesion may be confused with a pedunculated malignant melanoma Microscopically the typical papilloma reveals pronounced acanthosis and varying degrees of keratinization dyskeratosis, and nonspecific inflammation

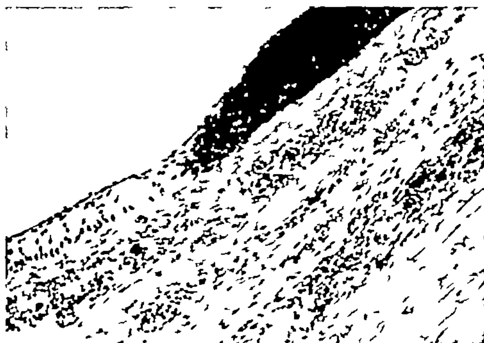
Carcinoma in Situ.—Carcinoma in situ of the bulbar conjunctiva varies considerably in its clinical appearance It may present as an area of leukoplakia, as a papilloma or as a complication of pterygium or pinguecula The histopathologic characteristics of carcinoma in situ of the conjunctiva and cornea are similar to those observed elsewhere in the mucous membranes (Fig 1049) or the lesion may mimic Bowen s disease of the skin (Fig 1050)

Squamous Cell Carcinoma.—Squamous cell carcinoma is encountered on the bulbar conjunctiva and cornea, but basal cell carcinoma arising in these tissues is of questionable occurrence Clinically significant infiltrative carcinoma (Fig 1051) is seldom observed in the United States probably because it is a common practice to excise, for cosmetic or other reasons, early precancerous or in situ cancerous lesions long before they become infiltrative. Such lesions as well as the majority of early invasive cancers of the limbal area can be adequately controlled by excisional therapy Rarely, in this country, is it necessary to resort to radical surgery for these tumors (Fig 1052) We have been impressed, however by the comparative frequency of large much more advanced infiltrative cancers of the conjunctiva and cornea which have been received from certain Asiatic countries through the facilities of the Registry of Geographic Pathology of the Armed Forces Institute of Pathology Whether this is a consequence of biologic or sociologic differences we do not know

Malignant Melanoma —Malignant melanoma of the conjunctiva and cornea may arise without an apparent precursor lesion or it may be a sequella of a nevus or of precancerous melanosis

Nevus Origin —Nevi of the conjunctiva, according to Reese, seldom give rise to malignant melanoma. In his experience precancerous melanosis has been a much more common precursor In the Registry of Ophthalmic Pathology however there are many good examples of the occurrence of sudden growth during adult life of nevi known to have been present since childhood (Fig 1053) Histologically these tumors have also shown evidence of the occurrence of malignant change in previously benign compound nevi. The subsequent behavior of these histologically malignant melanomas has been difficult to predict. Many particularly the pedunculated limbal lesions, have neither recurred nor metastasized even though removed by simple excision. Others have produced multiple recurrences and at least one (Fig 1054) has even metastasized without killing the patient (Lewis and Zimmerman) Those which arise in or about the caruncle, like those of the palpebral conjunctiva seem to have a worse prognosis than those of the limbal region Unfortunately however these statements cannot yet be documented by good follow up data of a significant series of adequately studied cases

Precancerous Melanosis —Precancerous melanosis has been differentiated from other pigmented lesions of the conjunctiva by Reese, mainly on the basis of its important clinical characteristics. It differs from conjunctival nevi by its late oc



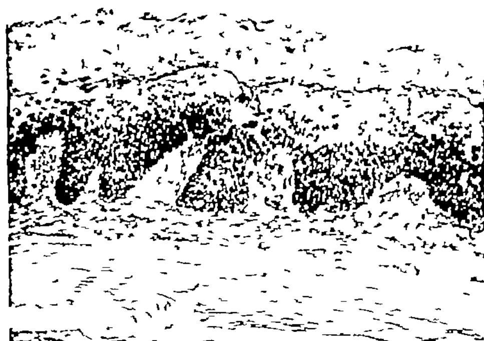


Fig 1049 —Carcinoma in situ. There is an abrupt transition from essentially normal conjunctival epithelium to the intraepithelial neoplasm The tumor in this case is more cellular but much less pleomorphic than the one shown in Fig. 1050 H. and E stain. (×160.) (AFIP Acc. 272972)

Fig 1050 —Carcinoma in situ. The conjunctiva is markedly thickened by extremely pleomorphic cells. The process extended onto the cornea and the eye was enucleated H and E. stain. (×90) (AFIP Acc. 238743)





Fig 1051 —Carcinoma of the limbus The tumor has infiltrated the stroma of the corneoscleral limbus and has extended along the aqueous outflow pathways into the anterior chamber angle a very unusual complication of limbal tumors. H. and E stain (×50) (AFIP Acc. 690246)

Fig 1052 —Carcinoma of the limbus. This tumor presents a more characteristic picture than that shown in Fig. 1051 An exophytic growth pattern with the formation of a papillomatous mass is typical of the more advanced limbal carcinomas. Even in such large tumors, the corneoscleral stroma tends to prevent the neoplasm from invading the intraocular tissues. H. and E stain. (×18) (AFIP Acc. 785865)

currence (typically in the fifth decade) its diffuse, nonelevated granular appearance, its ill-defined borders, and its comparatively poor prognosis due to the frequency with which it gives rise to metastasizing malignant melanoma. Usually a long period of 5 to 10 years elapses between the onset of precancerous melanosis and the development of malignant melanoma During this interval the extent of the lesion and the degree of pigmentation may fluctuate spontaneously or as a result of radiation therapy The disease affects the bulbar conjunctiva most commonly but associated lesions of the cornea, palpebral conjunctiva, and skin of the lids are not uncommon.



Fig. 1053—Malignant melanoma arising in a nevus known to have been present since childhood. The patient, a 59-year-old white woman, stated that the lesion suddenly became quite large several months before it was excised. H. and E. stain. (×135.) (AFIP Acc. 643700.)

Histologically precancerous melanosis appears as a diffuse infiltration of the conjunctival epithelium by nests of nevus cells with varying degrees of pleomorphism, pigmentation and chronic inflammation (Fig 1055) Typically the subepithelial nests of nevus cells and associated cystic epithelial inclusion so frequently seen in conjunctival nevi are absent in precancerous melanosis.

The transition from the precancerous to the cancerous state may not be apparent clinically though usually there are areas which become elevated nodular ulcerated and/or more deeply pigmented Reese estimates that at least 40 per cent of his cases of cancerous melanosis (malignant melanoma arising in an area of precancerous melanosis) die of metastasis He therefore recommends that repeated biopsies of suspicious areas be made during the precancerous state, and that when histopathologic evidence of malignant change is obtained, exenteration be performed

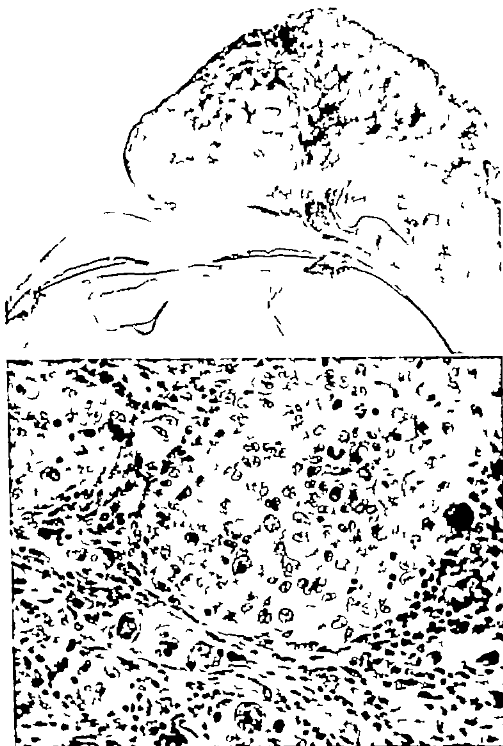


Fig. 1054.—Large pedunculated malignant melanoma of the limbus in a 44-year-old Negro woman. Amputation of one leg because of metastasis was performed nine years after enucleation, but the patient was living without other evidence of metastatic disease sixteen years later. H and E. stain. (*A* ×6. *B* ×305.) (AFIP Acc. 35659.)



Fig 1055.—Precancerous melanosis. The patient, a 55-year-old white woman, had observed progressive pathologic pigmentation of her bulbar conjunctiva and cornea over a three-year period. In addition to the widespread intraepithelial proliferation of nevus cells, there is a diffuse chronic inflammatory reaction of the subepithelial tissues. H and E. stain. (×150.) (AFIP Acc. 596399.)

INTRAOCULAR TISSUES

Surgical pathology of the eye itself differs from most of the rest of surgical pathology for several important reasons. In the first place, biopsies of intraocular tissues are rarely feasible. The only important exception is in the case of iris lesions which often can be completely excised, or at least biopsied by iridectomy. It is true that cataracts are commonly removed but in very few hospitals are they routinely submitted for histopathologic study. The reasons for this are several: (1) the procedure of cataract extraction itself produces severe morphologic alterations which tend to obscure the primary lens damage, (2) relatively little can be determined as to etiology and pathogenesis of cataracts by microscopic examination, and (3) rarely does histopathologic study of lenses with cataracts furnish information of clinical or prognostic importance.

Most of the eyes reaching the surgical pathology laboratory are obtained as a result of enucleation. Usually the globe is intact but free of such accessory tissues as the extraocular muscles and orbital fat. Much less often the eye is eviscerated and only fragments of the intraocular tissues are submitted for microscopic study. In such cases it is rarely possible to arrive at a satisfactory diagnosis and clinicopathologic correlation. Eyes which are enucleated or eviscerated have usually been diseased for a long period of time and have become blind. Severe pain and unsightliness are the common immediate reasons for removing the eye. In these cases it is the responsibility of the pathologist, not merely to arrive at a definitive

diagnosis, but to reconstruct the sequence of events that took place from the onset of ocular disease to the final stages which led to enucleation

This brings us to another distinctive characteristic of ophthalmic pathology Frequently the initial pathologic process becomes completely obscured by the subsequent series of events For example, the patient may first complain of visual disturbance produced by a cataract The lens opacification progresses and cataract extraction is performed Defective wound healing follows and surface epithelium grows down into the anterior chamber This leads to secondary glaucoma for which one or more additional surgical procedures are performed These in turn may be complicated by hemorrhage infection or retinal detachment Finally the eye may become shrunken (phthisical) and disfiguring A period of several years to a decade or more usually is required for such a series of events to take place

Intraocular neoplasms represent an exception to the generalizations just given. Since only in the case of iris tumors is it ordinarily possible to excise the neoplasm, the procedure usually followed is to recommend early enucleation for other uveal and retinal neoplasms. The aim here is to arrive at a correct clinical diagnosis early, long before such secondary pathologic processes as cataract formation massive retinal detachment, glaucoma uveitis or phthisis complicate the picture. Therefore, the pathologist often observes a much less confusing array of pathologic changes and has a much easier job in the case of eyes removed because of intraocular neoplasms than he has with other enucleated eyes This however, is not invariably the case, for if the tumor has been present and growing for a long period of time it too may lead to a wide assortment of secondary processes which sometimes confuse the pathologist as well as the clinician

In the case of orbital neoplasms it often becomes necessary to remove an essentially normal eye along with the other intraorbital structures in a block dissection. This operation is called exenteration of the orbit.

Another characteristic of ophthalmic pathology concerns the diverse and sometimes unique tissues encountered in the eye Not only does the eye combine neural, epithelial, and connective tissues in a complex manner, but it presents several tissues which are normally avascular and therefore capable of responding to irritants in a very limited fashion The lens, for example, is a highly modified piece of surface ectoderm devoid of all supporting connective tissue stroma and blood vessels. The cornea and vitreous are also avascular, but these are largely mesenchymal structures which possess an abundance of acid mucopolysaccharide The retina offers an even more peculiar situation in relation to its blood supply for its inner and outer halves are very different in this respect. The outer layers of the retina are avascular and the visual cells derive their nutrients and oxygen not from the retinal circulation but from the choroidal capillaries (choriocapillaris) The nerve fiber ganglion cell and inner nuclear layers, on the other hand, are supplied by the retinal capillaries. Lesions affecting the choroidal circulation therefore tend to damage the visual cells while diseases of the retinal vessels produce maximal effects on the ganglion cells and nerve fibers

Related to the multiplicity of tissues and their anatomical chemical, and physical peculiarities are the diverse reaction patterns observed in different portions of a given eye. The ophthalmic pathologist is constantly faced with the problem

Retrolental Fibroplasia.—Retrolental fibroplasia also called the retinopathy of prematurity is an acquired form of developmental disorder resulting from the unique sensitivity of retinal blood vessels of the premature retina to oxygen (Reese) Normally the retinal blood vessels complete their development shortly before birth. Much of the retinal periphery of a baby born after only 6 or 7 months of gestation is completely avascular If such a premature baby is given high concentrations of oxygen (over 40 per cent) normal vascularization of the retinal periphery may

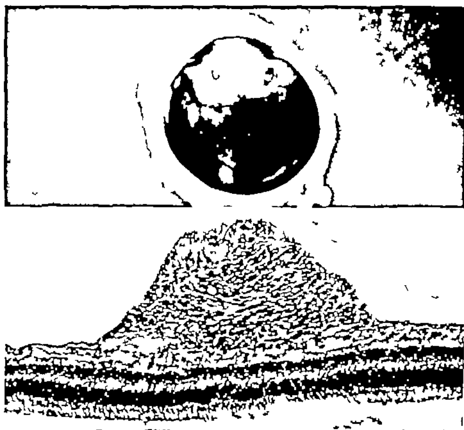


Fig 1058 —Retrolental fibroplasia (retinopathy of prematurity) An opaque mass consisting of organized vitreous and the completely detached retina are present immediately behind the lens. (AFIP Acc. 597231)

Fig 1059 —Tuberous sclerosis. A glial nodule or hamartoma projects against the vitreous body from the nerve fiber layer of the retina. H and E. stain (×90) (AFIP Acc. 511046)

be inhibited. Vasoconstriction and actual obliteration of the terminal vessels may follow prolonged oxygen therapy Later upon withdrawal of oxygen, pathologic neovascularization occurs. These newly formed vessels frequently invade the vitreous, leak serum or blood, and eventually lead to organization of the vitreous retinal detachment, and blindness (Fig 1058) Before the pathogenic and diagnostic significance of prematurity and oxygen therapy was realized, many of the affected eyes were enucleated because of the suspicion of retinoblastoma. The reason for this is that in both conditions a white opaque mass forms behind the lens. The mass produces a white pupil (leukokoria) and in the dark gives a "cat-eye reflex." Also a high incidence of bilaterality occurs in both conditions.

Phakomas.—Phakomas are hamartomatous malformations which often are associated with extraocular lesions as a part of well-defined clinicopathologic syndromes. These include Bourneville's syndrome (tuberous sclerosis) von Recklinghausen's disease (neurofibromatosis) the Sturge Weber syndrome (encephalotrigeminal angiomatosis) and von Hippel Lindau disease (angiogliomatosis) In



Fig 1060—Tuberous sclerosis. This large partially calcified glial hamartoma (called a giant drüsen) projecting from the optic disc had been suspected clinically to be a malignant tumor and for this reason the eye was enucleated *A* Gross appearance of the lesion. *B* Photomicrograph of same specimen. H and E stain. (×70) (AFIP Acc. 511046) (From Zimmerman, L. E., and Walsh F B Am. J Ophth 42 737 747 1956)

tuberous sclerosis the most characteristic intraocular lesions are glial plaques and nodules in the nerve fiber layer of the retina (Fig 1059) and calcified giant drüsen of the optic disc (Fig 1060) Neurofibromas (Fig 1061) and melanotic tumors of the uvea and gliomas of the optic nerve (see p 1019) are observed in von Reckling



Fig 1061 —Recklinghausen's disease Multiple neurofibromas of the uveal tract. (AFIP Acc. 30183) (From Callender G R. and Thigpen, C A Am. J Ophth. 13: 121 124 1930)

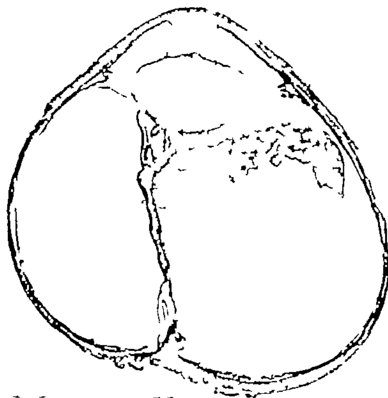


Fig 1062 —Von Hippel Lindau disease. Angiomatosis retinae has become complicated by vitreous hemorrhage organization, and retinal detachment. H and E stain. (×4) (AFIP Acc. 753398)

hausen's disease Hemangioma of the choroid (Fig 1010) is the most common intraocular lesion of the Sturge Weber syndrome Ipsilateral glaucoma and megaloglobus are commonly observed in the Sturge Weber syndrome and occasionally in von Recklinghausen's disease Abnormally large tortuous arteries and veins leading to a retinal nodule composed of vascular, endothelial, and glial tissues are characteristic of von Hippel Lindau disease (Fig 1062) Vitreous disturbance and retinal detachment are common complications

Trauma

Trauma necessitating removal of the globe is usually a penetrating or perforating injury Occasionally a severe contusion of the eye results in enough intraocular change, usually hemorrhage to require enucleation Massive hemorrhage if in the anterior chamber may cause intractable glaucoma or, if in the vitreous, may lead to phthisis bulbi These two conditions will be discussed later Chemical, thermal and other forms of injury are much less frequent

A penetrating or perforating wound of the globe may be so extensive as to cause complete disruption of the eye and require its immediate removal The majority of injured eyes however are removed at varying intervals because of secondary changes such as organization of hemorrhage glaucoma or inflammation Adequate histologic preparations of such specimens should reveal the sites of perforation as well as the secondary changes in other ocular tissues (Fig 1063) If the wound is anterior, the cornea iris and lens are usually involved if posterior the sclera, choroid and retina are chiefly affected Detachment of the retina is a common complication resulting from organization of exudate or hemorrhage. The lens is frequently lost through the wound dislocated or severely damaged (traumatic cataract) Progressive degeneration of the intraocular tissues may lead to phthisis bulbi

The presence of retained foreign bodies may give rise to important secondary changes. Organic matter such as pieces of vegetation, clothing and cilia generally provoke a more intense inflammatory reaction than do inorganic substances Some metallic foreign bodies particularly soft rusty iron and copper compounds may be very toxic and cause degenerative changes in a number of intraocular tissues (siderosis and chalcosis respectively)

Two important clinicopathologic syndromes which are generally complications of penetrating injury are sympathetic uveitis and phacoanaphylactic endophthalmitis. These will be considered in the following section on intraocular inflammations.

Inflammation

Inflammation of the eye as elsewhere may be either acute or chronic, granulomatous or nongranulomatous.

Acute Inflammation.—Acute intraocular inflammation is often but not always, infectious in origin. The causative organism is usually a bacterium and is generally introduced through a perforating wound but occasionally the infection is hematogenous (Fig 1064) Initially there is a massive purulent reaction in the anterior chamber and vitreous and the process is called endophthalmitis. As

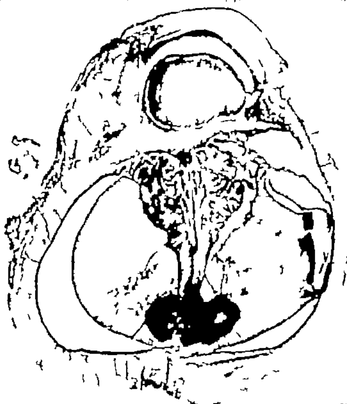


Fig 1063 —A penetrating wound of the eye and multiple minute intraocular foreign bodies (palm splinters) have led to the formation of a dense mass of inflammatory tissue in the anterior segment on one side Organization of the vitreous has been complicated by retinal detachment. Blood clots are attached to the stalk of the detached retina near the optic disc. H and E. stain. (×4) (AFIP Acc. 737587)

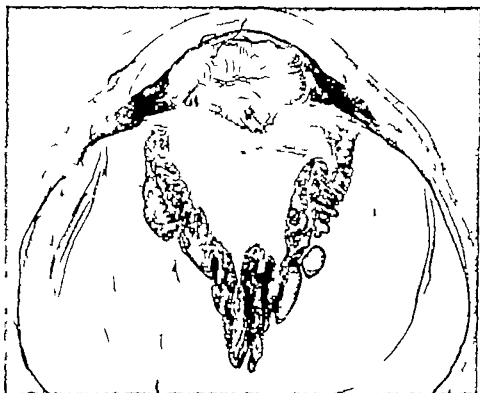


Fig 1064 —Endogenous endophthalmitis. This vitreous abscess developed as a consequence of meningococcic meningitis and led to retinal detachment. H. and E. stain. (×6.) (AFIP Acc. 35072.)

the infection spreads other intraocular tissues, such as the retina, uvea, and eventually the cornea and sclera may become involved At this stage the term panophthalmitis is applicable In the days before antibiotic therapy, eyes affected by severe panophthalmitis were frequently eviscerated or enucleated early Today, the infection can often be controlled but subsequent organization of the exudate leads to phthisis bulbi (see p 1052) A not unusual cause of noninfectious endophthalmitis or panophthalmitis is massive necrosis of a uveal malignant melanoma

Chronic Nongranulomatous Inflammation—In chronic nongranulomatous inflammation of the eye the uveal tract (iris ciliary body and choroid) is primarily involved. In anterior uveitis (iridocyclitis) the tissues are typically infiltrated by plasma cells in a rather diffuse fashion (Fig 1065) but occasionally we see nodular lymphocytic infiltrates In posterior uveitis (choroiditis) the round cell infiltration may also be diffuse, but frequently it is focal or scattered as multiple discrete lesions. In choroiditis the overlying retina is usually involved by spread of the inflammatory reaction hence the term chorioretinitis. In choroiditis even if prolonged, enucleation is not often necessary as these eyes do not become painful However with recurrent iridocyclitis the inflammatory reaction often produces adhesions between the iris and cornea (anterior synechiae) (Fig 1066) or between the iris and lens (posterior synechiae) (Fig 1067) and secondary glaucoma results. If this condition is intractable, enucleation is almost inevitable The etiology and pathogenesis of nongranulomatous uveitis can rarely be ascertained clinically or pathologically

Granulomatous Inflammation.—Granulomatous inflammation is often the result of a specific infection such as toxoplasmosis tuberculosis syphilis leprosy blastomycosis, or nematodiasis Sarcoidosis and the rheumatoid diseases are also important causes of granulomatous inflammation The inflammatory process in granulomatous uveitis may be diffuse but often there is a more localized area of destruction in which the causative agent or otherwise diagnostic lesion will be found. It is, therefore, of paramount importance that the gross specimen be examined carefully with the dissecting microscope (×7 magnification) in order that a small but important lesion will not be overlooked

The term "granulomatous uveitis is misleading for often the most diagnostic lesions are not found in the iris, ciliary body or choroid but rather in the retina, vitreous, or sclera. In certain diseases such as leprosy and sarcoidosis, the most significant lesions are typically located in the anterior segment (iris ciliary body cornea, and sclera) The diagnostic lesions of toxoplasmosis are found in the retina and choroid, those of nematodiasis in the vitreous or retina and those of the rheumatoid group in the sclera between the limbus and the equator In tuberculosis and fungus infections the lesions are less constant in location and appearance.

During recent years the studies of Wilder and other pathologists at the Armed Forces Institute of Pathology have established the fact that in enucleated eyes containing granulomatous lesions toxoplasmosis and nematodiasis together account for more cases than all other infections combined (Zimmerman) This statement is based principally upon those cases in which the causative agents have been demonstrated within the ocular lesions by histopathologic study Because of their







Fig 1065 —Nongranulomatous iritis. The atrophic iris is diffusely infiltrated by plasma cells and several Russell bodies are present. Irregular degenerative and proliferative changes are observed in the pigment epithelium. H and E. stain. (×360.) (AFIP Acc. 698722.)

Fig 1066 —Same case illustrated in Fig 1065 The chronically inflamed iris has become almost completely adherent to the cornea, and the anterior chamber is virtually obliterated H and E stain. (×8)

Fig 1067 —Nongranulomatous iritis with posterior synechiae The iris is firmly attached to the lens, which reveals widespread degeneration of its cortex and fibrous metaplasia of its subcapsular epithelium H and E stain. (×25) (AFIP Acc. 184111)

relative importance only the lesions of toxoplasmosis and nematodiasis will be described here

Toxoplasmosis.—Toxoplasmosis whether congenital or acquired tends to produce rather discrete chorioretinal lesions. The uveal tract including the iris and ciliary body often reveals diffuse infiltration by plasma cells and lymphocytes, but the destructive granulomatous lesions are typically restricted to the posterior half of the globe (Fig 1068). The morphologic pattern observed in these chorioretinal lesions is highly characteristic. Most important diagnostically is a focal abruptly delineated area of coagulative necrosis of the retina (Fig 1069). Frequently this important part of the retina becomes greatly reduced in thickness and very friable so that there is a great danger of its being lost or fragmented during preparation of the sections. In this area of infarctlike retinal necrosis most of the nuclei of retinal cells have vanished or only their ghostly outlines remain. Very few inflammatory cells are present but many pigment granules may be strewn about from the necrotic pigment epithelium. It is in this necrotic retinal tissue that the proliferative forms and cysts of *Toxoplasma gondii* will be found upon careful oil immersion microscopy (Fig 1070).

The choroid and sclera immediately adjacent to the area of retinal necrosis are typically thickened and massively infiltrated by epithelioid cells lymphocytes and plasma cells. In some cases there is also much episcleral reaction so that an epibulbar nodule is formed (Fig 1068).

Nematodiasis.—Nematodiasis is a broad term encompassing a variety of parasitic diseases. The one form of ocular nematodiasis which has been found with considerable frequency in the United States is a type of visceral larva migrans, probably produced in most cases by wandering larvae of *Toxocara canis* (Beaver). This is principally an infection of children between the ages of 3 and 10 years. Almost without exception those children who have had ocular infection have not had clinical evidence of systemic visceral larva migrans and those who have had the systemic form have not had ocular lesions. Typically a single migrating larva finds its way hematogenously into the eye and comes to rest in the vitreous or on the inner surface of the retina (Fig 1071).

A pronounced infiltration by acute and chronic inflammatory cells, often with intense eosinophilia is observed in these tissues but the uveal tract is often remarkably uninvolved. Presumably because of the freedom of uveal inflammation, the eye is usually asymptomatic. Eventually the inflammatory reaction in the vitreous leads to organization and contracture of this structure with consequent detachment of the retina (Fig 1072). This leads to a whitening of the pupil (leukokoria) and the observation of a cat-eye reflex in the dark. Retinoblastoma is frequently suspected and the eye is usually enucleated. Other cases are detected only when upon routine examination (often by the school nurse) the eye is found to be blind.

As the nematode larvae die they often stimulate the formation of a typical granulomatous inflammatory reaction about them. It is usually necessary to make serial sections to find these minute granulomas. The typical inflammatory reaction with intense eosinophilia observed in the vitreous is presumptive evidence of nematodiasis but the larvae must be found to establish a definitive diagnosis.

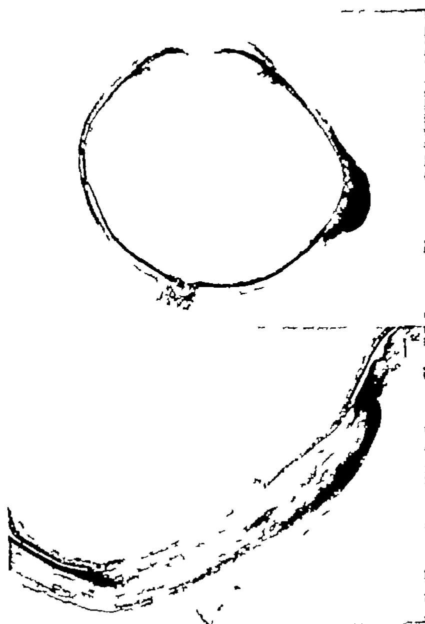


Fig. 1068.—Granulomatous chorioretinitis, scleritis, and episcleritis due to toxoplasmosis. This type of segmental involvement of all ocular coats posterior to the equator, with the formation of an epibulbar nodule of inflammatory tissue is extremely characteristic of toxoplasmosis. H and E stain (×2.) (AFIP Acc. 70313.) (From Wilder H C.: A. M. A. Arch. Ophth. 48: 127-136, 1952.)

Fig. 1069.—Sharply outlined area of coagulative retinal necrosis with necrosis and granulomatous inflammation of the immediately adjacent choroid, sclera and episclera, are typical of toxoplasmosis. It is in the necrotic retina that the parasites are found (Fig. 1070). H and E. stain. (×7.) (AFIP Acc. 754058.)

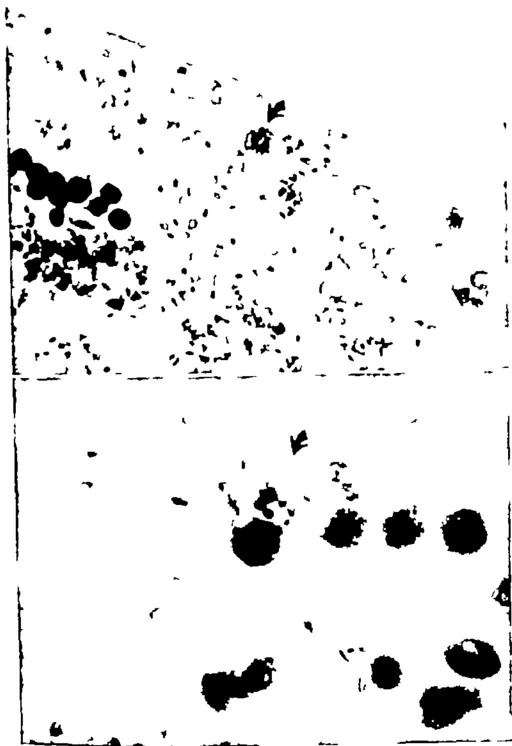
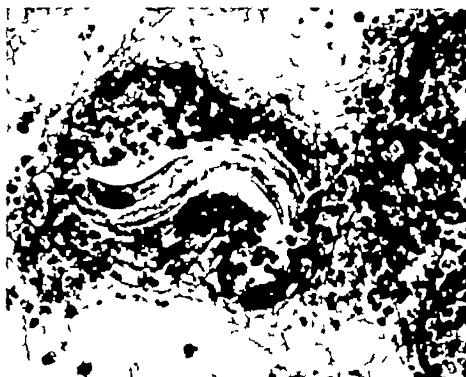


Fig 1070—Encysting proliferative forms *(arrows)* of *Toxoplasma gondii* found in the necrotic retina of lesion shown in Fig 1069 H and E. stain. (*A* ×1000 *B* ×2000) (AFIP Acc. 754058) The small particles observed in these photographs are pigment granules from the necrotic retinal pigment epithelium, while the larger round structures represent pyknotic retinal nuclei.



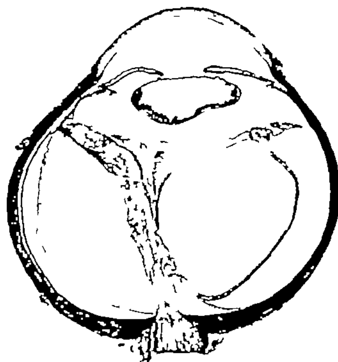


Fig 1071.—Nematode larva, probably *Toxocara canis* surrounded by inflammatory cells in the vitreous body H and E. stain (×220) (AFIP Acc. 298563)

Fig. 1072.—Nematode endophthalmitis. The inflammatory reaction in the vitreous body has led to retinal detachment. H and E stain. (×3) (AFIP Acc. 198761) (From Wilder H. C. Tr Am. Acad Ophth. 54: 99-109 1950.)

Posttraumatic Uveitis.—Following penetrating injury of the eye the development of a granulomatous uveitis always causes great concern because of the possibility of sympathetic uveitis a dreaded disease in which injury to one eye gives rise to severe inflammation which sometimes progresses to blindness in the uninjured eye as well as in the injured eye Other causes of posttraumatic granulomatous inflammation are lens induced endophthalmitis (phacoanaphylaxis), foreign bodies and blood in the vitreous



Fig 1073—Sympathetic uveitis There is a diffuse nonnecrotizing granulomatous reaction involving the entire uveal tract but sparing other ocular tissues. H and E stain. (×3) (AFIP Acc 105961) (From Friedenwald J et al Ophthalmic Pathology An Atlas and Textbook, Philadelphia 1952 W B Saunders Co)

Sympathetic Uveitis—Sympathetic uveitis is probably the best example we have of a pure granulomatous uveitis for the significant lesion in this disease is confined to the uveal tissues Typically the process involves the entire uveal tract (Fig 1073) There may of course be associated inflammatory lesions in other tissues due to the original trauma the presence of foreign bodies, etc. but the reaction of sympathetic uveitis itself is purely uveal There is a dense diffuse infiltration of the choroid by lymphocytes (Fig 1074) and often the ciliary body and iris are similarly involved Superimposed upon this lymphocytic infiltrate are small, irregular patchy accumulations of large pale staining epithelioid cells which upon high magnification will often be found to contain finely dispersed melanin granules (Fig 1075) Variable numbers of plasma cells and eosinophils may be included, but polymorphonuclear leukocytes are characteristically lacking The reaction involves the outer and middle coats of the choroid extending into the scleral canals along ciliary vessels and nerves, sometimes to the episcleral surface The choriocapillaris on the other hand is typically uninvolved

Phacoanaphylaxis—Phacoanaphylactic endophthalmitis usually follows penetrating injury to the lens but a few cases have been observed following spon

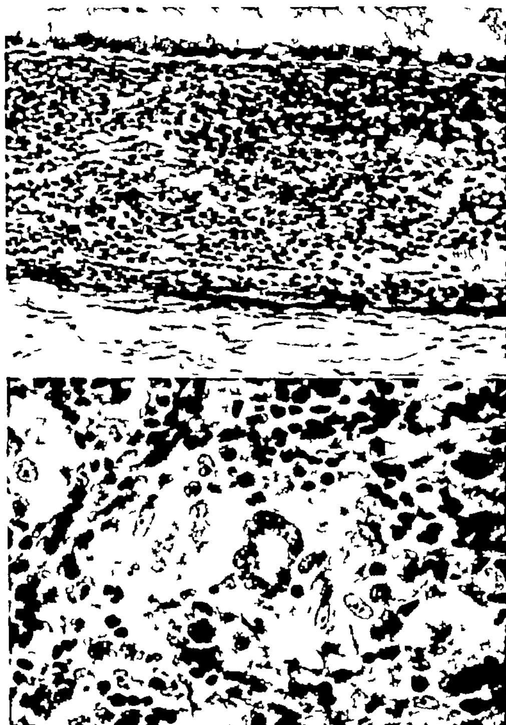


Fig. 1074.—Sympathetic uveitis. The uveal tissues are diffusely infiltrated by lymphocytes, and there are small irregular collections of pale-staining epithelioid cells. H. and E. stain. (×300.) (AFIP Acc. 731769.)

Fig. 1075.—Epithelioid cells and giant cells containing finely dispersed uveal pigment granules are characteristically present in sympathetic uveitis. H. and E. stain. (×655.) (AFIP Acc. 37381.) (From Friedenwald, J., et al.: Ophthalmic Pathology. An Atlas and Textbook, Philadelphia, 1952, W. B. Saunders Co.)

tanéous rupture of a swollen cataractous lens. It is characterized by a granulomatous inflammatory reaction centered about an area of lens perforation. The process is believed to be the result of acquired hypersensitivity to lens protein (Verhoeff). A typical zonal pattern of inflammatory reaction is observed in most cases (Fig. 1076). In the area where the lens capsule is broken there is a massive

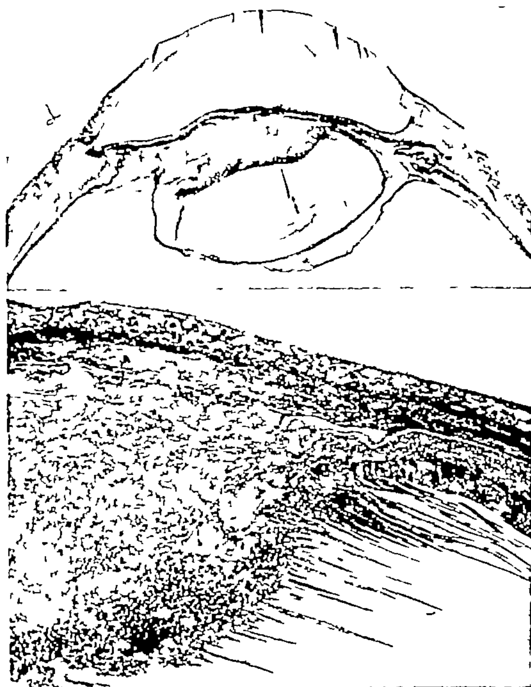


Fig. 1076.—Phacoanaphylactic endophthalmitis. A penetrating wound has ruptured the anterior lens capsule. A dense infiltrate of acute and chronic inflammatory cells is present in the area of lens damage. H and E stain. (×10.) (AFIP Acc. 339621.)

Fig. 1077.—Higher magnification of lesion illustrated in Fig. 1076. Polymorphonuclear leukocytes are present in and about the disintegrating lens fibers. Peripheral to them is a wall of macrophages, epithelioid cells and giant cells, and about the entire lesion there is a broad zone of granulation tissue. H and E stain. (×53.)

invasion of the lens by inflammatory cells. Centrally and immediately surrounding individual lens fibers there are polymorphonuclear leukocytes. Peripheral to this is a wall of epithelioid and giant cells about which is a broader more diffuse zone of granulation tissue and round cell infiltration (Fig 1077). The iris reveals a variable degree of plasma cell infiltration and posterior synechiae are commonly formed. Ordinarily the posterior uveal tract is not inflamed. In a considerable number of cases, however, phacoanaphylactic endophthalmitis and sympathetic uveitis are coexistent.



Fig 1078.—Phthisis bulbi. The globe is markedly shrunken, the sclera is wrinkled, and all intraocular tissues reveal severe degenerative changes. H and E. stain. (×7½.) (AFIP Acc. ?76925.)

Degeneration

Degenerative changes are common in the eye. Mostly they are the result of other primary processes such as trauma or inflammation. The most advanced stage of ocular degeneration in which all tissues are involved is called phthisis bulbi.

Phthisis Bulbi.—Phthisis bulbi represents the final stage of ocular degeneration in which the production of aqueous humor is so markedly reduced that the intraocular pressure falls (hypotony) and the globe shrinks (Fig 1078). The causes of phthisis bulbi are myriad, but most phthisical eyes reaching the laboratory of surgical pathology have been injured, either accidentally or as a result of surgical procedures. Phthisical eyes are enucleated for several reasons. Many are enucleated because they are disfiguring. Others become irritable because of periodic hemorrhages or bouts of uveitis. Some are enucleated for prophylactic reasons—the fear

of sympathetic uveitis or of malignant melanoma either of which may develop long after the eye has become blind and phthisical

All tissues are affected to varying degrees in phthisis bulbi and the degree of shrinkage is also variable The eye may be soft and spongy or stony hard due to calcification and ossification Typically the media are opaque Corneal scars exudates in the anterior and posterior chambers and advanced cataract formation prevent visualization of the inner eye The vitreous is usually destroyed and the retina completely detached. Extensive areas of osseous metaplasia are frequently observed along the inner surface of the choroid posteriorly (Fig 1079) The uvea is often edematous and pools of serous exudate may separate it from the wrinkled sclera

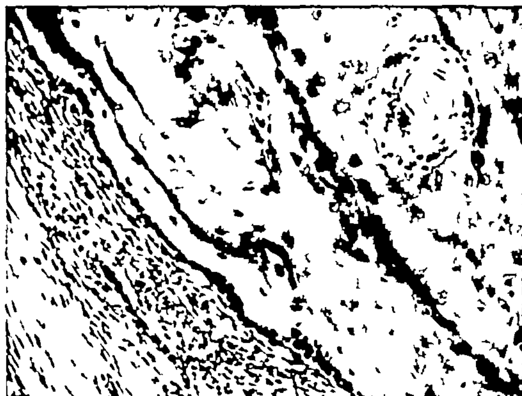


Fig. 1079—Osseous metaplasia is frequently observed in phthisical eyes H and E stain (×170) (AFIP Acc. 604006)

In those cases of phthisis bulbi which have followed extensive endophthalmitis or panophthalmitis, the various intraocular tissues often are so necrotic and replaced by scar tissue that most of the internal architecture of the eye is effaced

Glaucoma.—Glaucoma is conveniently placed here since it represents another condition of diverse etiology characterized by widespread degeneration of ocular tissues. The essential feature of the glaucomas is an unphysiologic state of increased intraocular pressure, due in almost all cases to impaired outflow of aqueous humor When the pathogenesis of the impaired aqueous drainage can be determined, we speak of *secondary glaucoma* but when the site of obstruction or the mechanics of its development remain obscure, the condition is called *primary glaucoma.*

Aqueous humor is produced by the ciliary processes and discharged into the posterior chamber. It flows forward between the lens and iris through the pupil, into the anterior chamber. *Aqueous humor leaves the anterior chamber via the* trabecular meshwork which is present in the deep layers of the peripheral cornea, just in front of the anterior chamber angle (Fig 1080). After passing through the trabecula, aqueous humor enters the canal of Schlemm and leaves the eye via the plexus of intrascleral and episcleral veins along the corneoscleral limbus.



Fig 1080.—Normal outflow channels for the passage of aqueous humor from the anterior chamber angle *(a)* include the corneoscleral trabecula *(t)*, Schlemm's canal *(c)* and the intrascleral plexus of veins *(v)*. Verhoeff-van Gieson stain. (×70.) (AFIP Acc. 630832.)

Secondary Glaucoma.—Secondary glaucoma may be a complication of numerous primary processes including trauma, inflammation, neoplasia, and malformation. The sites of obstruction to the outflow of aqueous humor are numerous, but the most vulnerable areas are the pupil and the angle of the anterior chamber. Formation of pupillary membranes as a result of organization of hemorrhages and exudates or the development of extensive adhesions between the iris and lens (posterior synechiae) as a consequence of iritis (Fig 1067) are the usual mechanisms leading to pupillary obstruction.

The outflow channels in the anterior chamber angle may become obstructed by particulate matter or by the formation of extensive adhesions between the root of the iris and the peripheral cornea (anterior synechiae). Particulate matter clogging the passages between the anterior cha[illegible] the canal of Schlemm is

usually cellular—red blood cells after massive hemorrhage into the anterior chamber leukocytes in certain types of uveitis (Fig 1081), tumor cells particularly with diffuse melanomas of the iris (Fig 1082), etc.

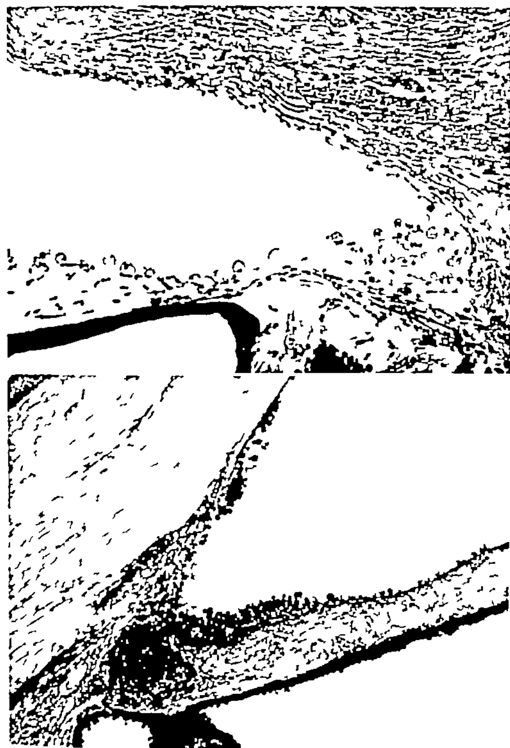


Fig 1081 —Outflow channels are blocked by macrophages in the anterior chamber in a case of phacolytic glaucoma (glaucoma secondary to lysis and escape of lens protein into the aqueous humor) H and E stain (×75) (AFIP Acc 609970) (From Flocks, M Littwin, C S and Zimmerman L E A M A. Arch Ophth 54 37-45 1955)

Fig 1082 —The anterior chamber angle and outflow channels are filled with deeply pigmented cells dispersed into the aqueous humor from a malignant melanoma of the iris. H and E. stain. (×50) (AFIP Acc. 176188)

Primary Glaucoma.—Primary glaucoma is idiopathic but certainly not always of similar nature. Several clinicopathologic forms of primary glaucoma are recognized chronic simple glaucoma, due in all probability to degenerative changes in the connective tissues about Schlemm's canal acute angle closure glaucoma, due in part to anatomic and physiologic peculiarities of the tissues of the anterior chamber

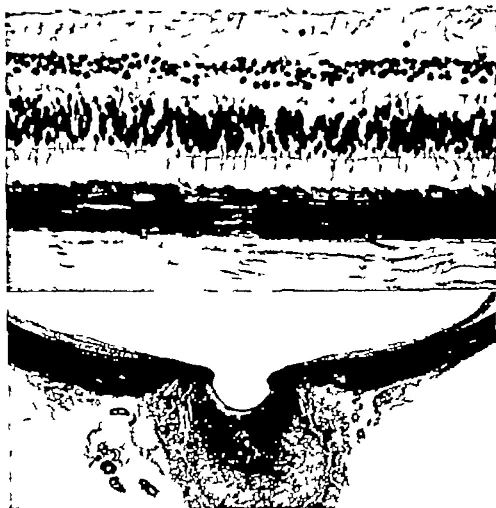


Fig 1083—The retina in chronic glaucoma reveals a widespread loss of ganglion cells and nerve fibers a reduction of cells in the inner nuclear layer but relatively well preserved visual cells. H and E. stain. (×230) (AFIP Acc. 49729) (From Friedenwald, J., et al Ophthalmic Pathology An Atlas and Textbook, Philadelphia, 1952 W B. Saunders Co.)

Fig 1084—Deep excavation (cupping) of the optic disc and severe atrophy of the optic nerve are important complications of chronic glaucoma. H. and E. stain. (×12.) (AFIP Acc. 57210)

which predispose to blockage of the anterior chamber angle by the iris root, without necessarily forming peripheral anterior synechiae and hypersecretion glaucoma a rare type in which the formation of aqueous humor exceeds the normal capabilities of the drainage mechanisms.

Regardless of the type and cause of glaucoma, certain degenerative changes are typically produced after periods of variable duration When glaucoma begins

in childhood the tissues tend to stretch and the globe may become greatly enlarged (buphthalmos), but when its onset is in adult life the tissues tend to resist stretching and normal ocular dimensions are maintained. The elevated intraocular pressure typically affects the inner retinal layers to a much more pronounced degree than it does the outer layers. A common observation is the presence of rather well preserved rods and cones and an intact outer nuclear layer when virtually all ganglion cells have disappeared and the nerve fiber and inner nuclear layers have become reduced to one half or one third their normal thickness (Fig 1083). Degeneration of nerve fibers is especially noteworthy in the region of the optic disc. This leads to excavation or cupping of the nerve head, posterior bowing of the lamina cribrosa, and severe atrophy of the optic nerve (Fig 1084). The uveal tract is usually very atrophic. Often discrete areas of scleral ectasia are observed, particularly in the equatorial regions. These are lined by uveal tissue and therefore have a bluish color—hence the name staphyloma (grapelike swelling).

Neoplasms

Neoplasms of the intraocular tissues are neither numerous in type nor of frequent occurrence. From a practical standpoint discussion may be limited to those arising from the melanocytic cells of the uvea, to retinoblastoma, and to metastatic carcinoma. For the sake of completeness a few remarks will also be made about hamartomatous lesions and certain rare tumors.

Malignant Melanoma.—Melanomas arising from the pigmented or potentially pigment producing cells of the uvea are by far the most frequent of all intraocular neoplasms except during the first decade. These tumors seem to be derived from, and to mimic in their growth patterns, two types of cells believed to be of neurectodermal origin. One is the stromal melanocyte which is present throughout the iris, ciliary body and choroid and which also is found in the scleral canals. The other is the Schwann cell of ciliary nerves. Certain tumors appear to be rather purely of one or the other type but more often than not various portions of the same tumor will present such morphologic differences that the simple classification into schwannian and stromal melanomas proposed by Reese is difficult to use. We have, therefore, continued to employ the Callender classification which has stood the test of time in the Registry of Ophthalmic Pathology and elsewhere. Callender's classification is based primarily on the cytologic characteristics of the tumors. Its validity is derived from the differences in prognostic significance of each type of tumor. Three main cell types are recognized, from their combinations and patterns 6 tumor types are defined.

The cell types are spindle A, spindle B and epithelioid. Spindle A cells are rather slender, very benign appearing spindle-shaped cells which have relatively small fusiform nuclei and no nucleoli (Fig 1085). Frequently the chromatin is arranged in a linear fashion along the central axis of the nucleus. Spindle B cells are larger and more pleomorphic, merging on the one hand with spindle A cells and on the other with epithelioid cells. Typically they possess large ovoid nuclei containing prominent nucleoli (Fig 1086). Mitotic activity may be more marked. Epithelioid cells are still larger and more irregular (Fig 1087). They have an

abundance of cytoplasm and may be truly gigantic. Multinucleated forms are not unusual. The nuclei are large and their nucleoli often are strikingly prominent. In some tumors many bizarre nuclei may be seen. As might be anticipated from the cytologic characteristics of these different types of melanomatous tumors, the spindle A type is essentially a benign neoplasm while the epithelioid tumors are much more prone to metastasize.

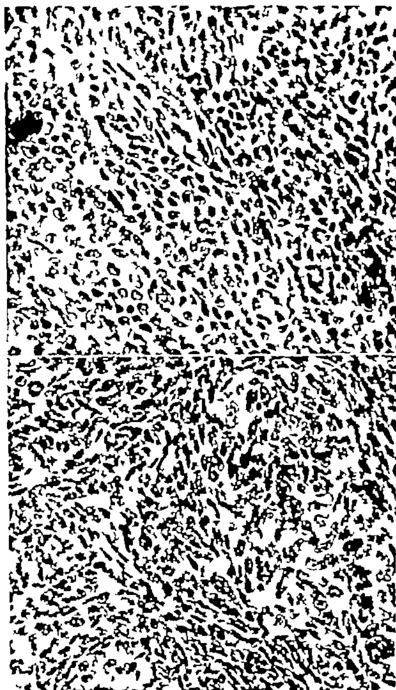


Fig. 1085.—Spindle A type of melanoma cells. H. and E. stain. (×510.) (AFIP Acc. 49801.)

Fig. 1086.—Spindle B type of melanoma cells are larger and more pleomorphic than spindle A cells. Most of the nuclei contain prominent nucleoli. H. and E. stain. (×305.) (AFIP Acc. 232296.)

It is rather unusual for these tumors to be composed of a single cell type. A mixture of spindle A and B cells or a mixture of spindle and epithelioid cells is very common. Certain of the spindle cell tumors present a fascicular pattern due to the palisading of nuclei (Figs. 1088 and 1089).

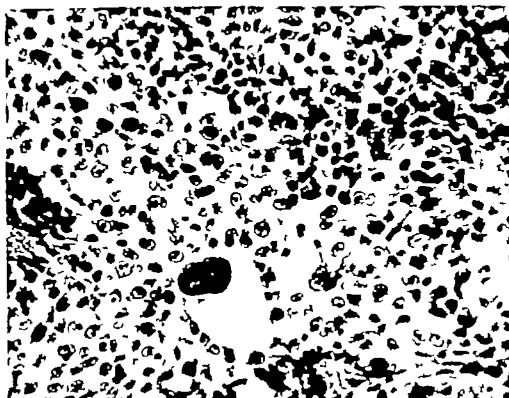


Fig. 1087.—Epithelioid type of melanoma cells are larger than the spindle cells and they contain more abundant cytoplasm, larger nuclei and more prominent nucleoli. H and E. stain. (×315.) (AFIP Acc. 190906.)

TABLE 46. PROGNOSIS OF 1,624 PATIENTS WITH MALIGNANT MELANOMA OF THE CHOROID AND CILIARY BODY

CELL TYPE	TOTAL CASES	5 YEAR MORTALITY (TUMOR DEATHS)
Spindle A	80	5%
Spindle B	519	13%
Fascicular	93	20%
Necrotic	129	45%
Mixed	749	52%
Epithelioid	54	69%
	1,624	

Table 46 presents the most recently compiled data based on the lengthy follow up studies of the Registry cases, and demonstrates the prognostic significance of the Callender classification.

Melanomas of the uvea exhibit great differences in pigment formation. There is a definite tendency for the most benign spindle cell tumors to be virtually amelanotic—another reason for believing them to be closely related to schwannian neoplasms. Conversely the most heavily pigmented uveal tumors are often more pleomorphic and more highly malignant. Unfortunately there are many exceptions to these generalizations.

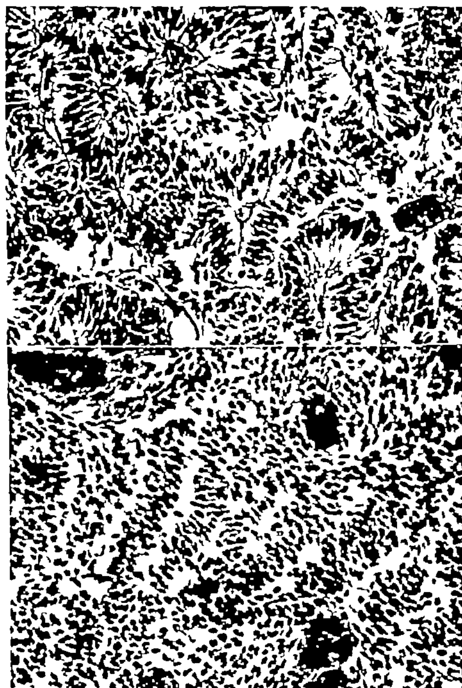


Fig 1088 —Fascicular type of melanoma composed of spindle cells arranged about dilated capillaries. H. and E. stain. (×250) (AFIP Acc. 231965)

Fig 1089 —Fascicular type of melanoma in which the spindle-shaped cells are arranged with their nuclei in parallel rows. H. and E stain. (×250) (AFIP Acc. 48427)



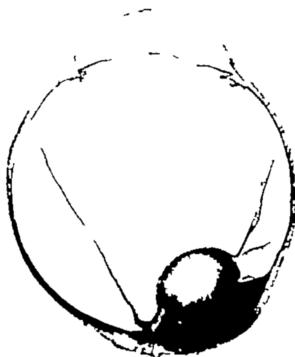


Fig. 1090—This malignant melanoma of the choroid has not broken through Bruch's membrane, but it has elevated the retina. Most of the retinal separation observed in this section is artifactitious. H and E. stain. (×3) (AFIP Acc. 79372.) (From Friedenwald, J., et al. Ophthalmic Pathology: An Atlas and Textbook, Philadelphia 1952, W B Saunders Co.)

Fig. 1091—By erupting through Bruch's membrane this malignant melanoma of the choroid has formed a mushroom-shaped subretinal mass. H. and E. stain. (×3) (AFIP Acc. 289600)



Fig 1092.—Massive orbital extension from a small choroidal melanoma has occurred as a result of diffuse spread along natural passages through the sclera and optic nerve. H. and E. stain. (×2.) (AFIP Acc. 159090) (From Friedenwald, J., et al.: Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, 1952, W B. Saunders Co.)

Fig. 1093.—This diffuse malignant melanoma of the ciliary body and choroid extended forward through scleral canals to form a large subconjunctival mass which encroached upon the cornea. H. and E. stain. (×9) (AFIP Acc. 824055)

Wilder showed that the amount of reticulum about individual tumors cells is also of prognostic significance, for those with a heavy fiber content tend to be more benign than do those with but little reticulum Flocks has shown that the size of choroidal and ciliary body melanomas at the time of enucleation is of considerable prognostic importance. Large tumors tend to contain epithelioid cells, and they have a decidedly worse prognosis than do small tumors which are typically pure spindle-celled neoplasms.

Another extremely important fact concerning the prognosis of uveal tumors is the very benign behavior of almost all neoplasms of the iris This is especially true of those iris tumors which are sufficiently small and localized to be excisable by iridectomy (Rones) Unfortunately, this fact is not sufficiently appreciated for all too often iridectomy is followed by enucleation of the eye when simple excision would have been sufficient.



Fig 1094—*Extensive necrosis of this large malignant melanoma produced a severe inflammatory reaction and secondary glaucoma.* (AFIP Acc. 829175)

Choroidal melanomas, regardless of their cytologic characteristics tend to grow inward as discoid, globular, or mushroom-shaped masses first elevating and then detaching the retina (Figs. 1090 and 1091) Less commonly they spread diffusely and extend out along scleral canals into the orbit (Figs. 1092 and 1093) Visual disturbance due to retinal detachment is therefore a much more frequent presenting complaint than is the formation of an orbital tumor Not infrequently the patient remains asymptomatic until the tumor has grown sufficiently to become necrotic and produce such complications as endophthalmitis, massive intraocular hemorrhage, and/or secondary glaucoma (Fig 1094) About 10 per cent of all malignant melanomas of the posterior uvea are not discovered until the enucleated eye is examined in the laboratory Iris tumors are much more often recognized early for they can be seen by the patient and his family long before other symptoms appear (Figs. 1095 and 1096)

Retinoblastoma.—Retinoblastoma is the most common intraocular neoplasm of children Generally believed to be congenital and derived from the incompletely differentiated retinal cells it nevertheless is seldom recognized until con

siderable growth has taken place. Ordinarily the neoplasm grows rather slowly and the child is about 2 years old when clinical manifestations become apparent. A few cases are not diagnosed until the second half of the first decade, but it is exceedingly rare to see retinoblastoma in patients older than this



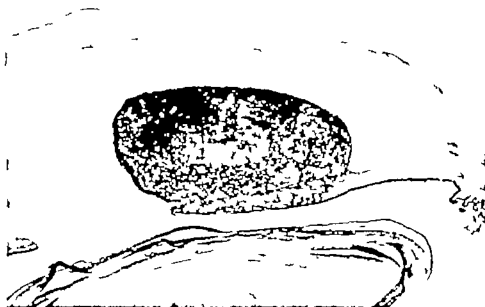
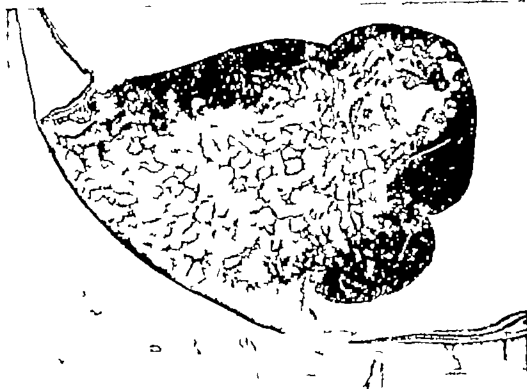


Fig 1095 —This tumor of the iris had been observed over a period of 10 years during which time it became progressively larger and encroached upon the pupil. Iridectomy revealed it to be of the spindle A cell type. The tumor recurred and necessitated enucleation for secondary glaucoma 15 years after iridectomy (AFIP Acc. 749919) (Courtesy Dr M. E. Nugent.)

Fig. 1096.—Melanoma of the iris frequently are clearly visible through the cornea hence their duration and rate of growth often are known by the patient or his family long before other subjective or objective manifestations appear H and E. stain. (×13) (AFIP Acc. 272658.)



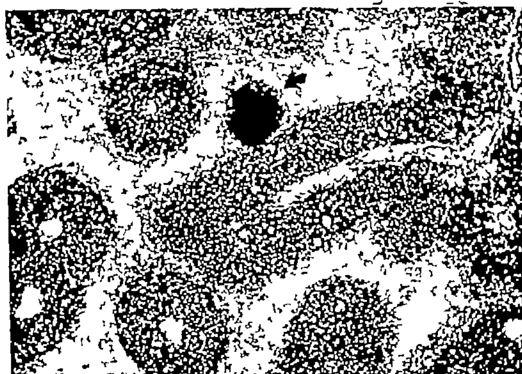


Fig 1097.—Retinoblastoma a highly cellular neoplasm with scanty stroma. The tumor tends to outgrow its blood supply and irregular areas of necrosis are commonly observed. H. and E. stain. (×12) (AFIP Acc. 747443)

Fig 1098.—Retinoblastoma. The typical pattern of a collar of viable cells about nutrient vessels is shown. Foci of calcification (*arrow*) occur within the areas of coagulation necrosis. H. and E. stain. (×80) (AFIP Acc. 147292)

Retinoblastomas are rarely rapidly growing neoplasms as long as they are confined to the retina and vitreous Ordinarily they are highly cellular and possess a scanty stroma (Fig. 1097) The tumor tends to outgrow its blood supply and necrosis is therefore extensive many minute foci of calcification are often present





Fig 1095.—This tumor o which time it became progressi vealed it to be of the spindle for secondary glaucoma 15 ye M. E. Nugent.)

Fig 1096.—Melanomas of hence their duration and rate o before other subjective or objecti Acc. 2 2658

in the areas of necrosis (Fig 1098) As the tumor grows it may protrude mainly into the vitreous (endophytic type) (Fig 1097) or outward between the retina and the pigment epithelium (exophytic type) (Fig 1099) Seeding is very common in both types, but the endophytic tumors tend to become disseminated throughout



Fig 1101—Bilateral retinoblastoma A white mass consisting of detached retina and neoplastic tissue is present immediately behind the lens in each eye. (AFIP Acc. 635460)

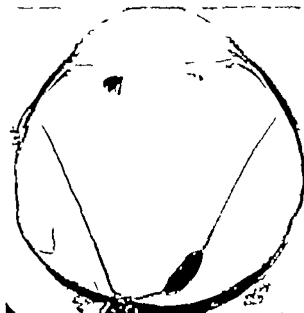




Fig 1102—This small retinoblastoma located in the macula produced a convergent strabismus which was first noted when the child was 12 months old The patient's twin also had a retinoblastoma. H and E stain. (×4) (AFIP Acc 260992)

Fig 1103—Extraocular extension of this retinoblastoma led to the formation of a huge orbital mass which produced proptosis of the eye (AFIP Acc. 519527)

the vitreous and even into the anterior segment while the exophytic neoplasms seed onto the pigment epithelium and gain access to the choroid. Both types tend to infiltrate the adjacent retina and extend into the optic nerve (Fig 1100)

Retinoblastomas, regardless of their growth patterns, frequently lead to the formation of an opaque white mass behind the lens (Fig 1101), the pupil there

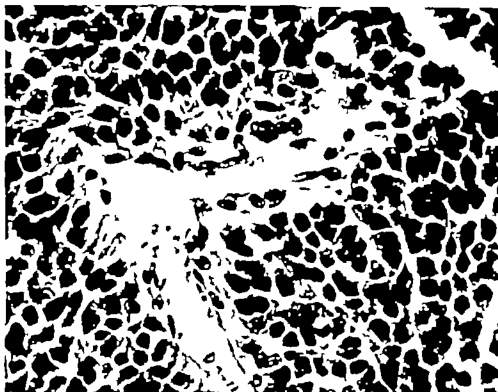


Fig. 1104.—Undifferentiated retinoblastomas composed of relatively large anaplastic cells have a less favorable prognosis than those which contain highly differentiated rosettes (Fig. 1105). H and E. stain. (×400.) (AFIP Acc. 190088.) (From Friedenwald, J., et al. Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, 1952, W. B. Saunders Co.)



Fig. 1105.—*A*, Well-differentiated retinoblastomas contain large numbers of rosettes which often are readily found even with very low magnification. H. and E. stain. (×50.) (AFIP Acc. 753671.) *B*, Higher magnification of tumor shown in Fig. 1097. H. and E. stain. (×200.) (AFIP Acc. 747445.)

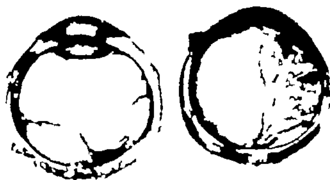


Fig. 1106.—Multicentric foci of neoplasia and bilateral involvement are commonly observed with retinoblastomas. (AFIP Acc 687292)

Fig 1107 —Metastatic carcinoma from the breast frequently produces diffuse thickening of the choroid posteriorly H and E. stain (*A* ×6 *B* ×48) (AFIP Acc. 638509)

fore appears white (leukokoria) in the daylight and gives a cat-eye reflex when examined in the dark.

Some retinoblastomas particularly those arising in the macular region (Fig 1102) produce blindness and consequent ocular deviation (squint) without causing massive retinal detachment or leukokoria. Rarely extraocular extension with the formation of an orbital mass is the presenting manifestation (Fig 1103)

Cytologically retinoblastomas may be indistinguishable from other neuroblastomatous neoplasms (Fig 1104) This is particularly true once they have extended into the choroid the orbit or the optic nerve Many of these retinal tumors, however are much more highly differentiated than are most neuroblastomas. In such well-differentiated retinoblastomas rosettes (Fig 1105) are commonly observed and they may be exceedingly numerous. Retinoblastomas of this type have also been called "neuroepitheliomatous retinal gliomas while the undifferentiated types have been called "medulloblastomatous retinal gliomas (Parkhill) The former have a better prognosis than the latter



Fig 1108 —Metastatic carcinoma may also produce bulky intraocular metastases. In this case the ocular metastasis was the first clinical evidence of a malignant tumor subsequently found to be primary in the lung. The patient, a 67-year-old white man, complained of visual loss and had had an operation for retinal detachment several weeks before enucleation. (AFIP Acc. 873092.)

A most important practical consideration for the surgical pathologist concerns examination of the optic nerve in order to determine the extent of invasion by the tumor (Fig 1100) Ordinarily the ophthalmic surgeon who suspects a retinoblastoma will try to obtain a long segment of optic nerve attached to the globe usually 10 to 15 mm Transverse sections of the nerve should be examined microscopically at the level of surgical transection and at various levels along the nerve. Tumors which have invaded the nerve and extended to the plane of transection or into the meninges have a bad prognosis. These tumors are very likely to extend along the nerve to the brain or be carried there by the subarachnoid fluid

Retinoblastomas often show multicentric foci of origin (Fig 1106) and bilateral involvement occurs in 20 to 30 per cent of the cases. The tumor frequently is much larger in one eye than in the other In some of these bilateral cases the less extensively involved eye can be successfully treated by radiation alone

(Reese, 1949 Stallard, 1955) or by a combination of radiation and chemotherapy (Reese 1958) The occurrence of an orbital or nasal neoplasm several years after successful radiation therapy of a retinoblastoma should lead one to suspect the possibility of an osteogenic sarcoma (Zimmerman)

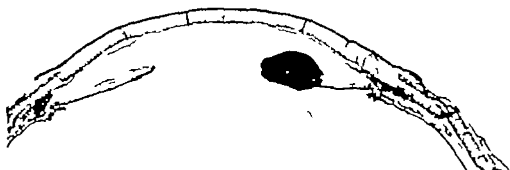


Fig 1109—Leiomyoma of the iris. This tumor of the papillary zone probably arose from the sphincter muscle. H and E stain. (×6) (AFIP Acc. 68490)

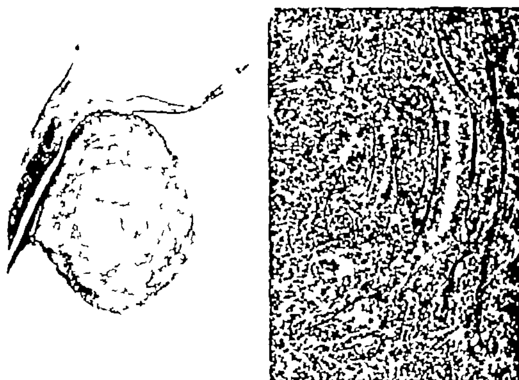


Fig 1110—Benign nonpigmented neuroepithelial tumor of ciliary body discovered after cataract extraction in a 55 year-old white woman. H and E. stain. (*A* ×9 *B* ×80) (AFIP Acc. 169585)

Metastatic Carcinoma.—Metastatic carcinoma is of some importance but sarcomas rarely spread to the inner eye Actually there are only two *forms* of cancer which metastasize to the eye with any degree of regularity mammary gland carcinoma in women and bronchogenic carcinoma in men The former is most likely to become a diagnostic problem when it metastasizes several years after mastectomy and no other clinical evidence of metastatic disease is found With

bronchogenic carcinoma the ocular metastasis is much more often a terminal event. Occasionally however, metastasis to the eye is the initial manifestation and the primary lesion is discovered only after the eye has been enucleated

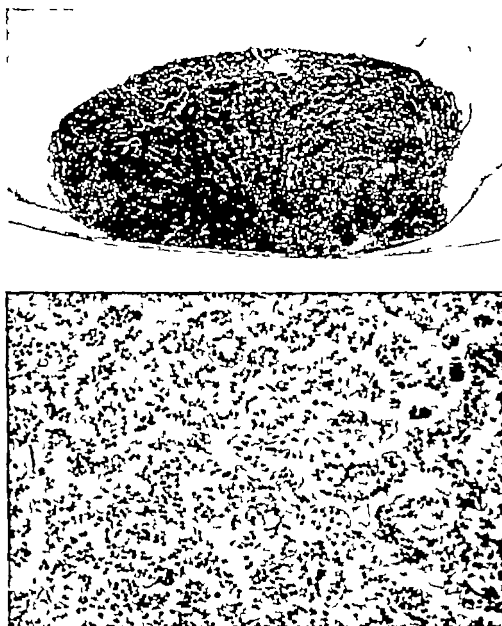


Fig. 1111 —This well-differentiated deeply pigmented tumor arising from the retinal pigment epithelium was considered to be of low grade malignancy. It had invaded the retina and choroid. The patient, a 57-year-old white woman, had complained of blurred vision for two months. H and E stain (*A* ×22 *B* after bleaching ×130) (AFIP Acc. 848819)

The posterior choroid is most often affected by metastatic carcinoma (Fig 1107) Anterior uveal involvement is much less common, and retinal metastases are rare. Although diffuse thickening of the choroid along both sides of the optic nerve is most characteristic, large bulky tumor masses resembling malignant melanomas may also be observed (Fig 1108)

Hamartomas.—Hamartomatous tumors including hemangiomas, neurofibro mas, and astrocytic nodules, may be isolated lesions or they may occur in one of the phakomatoses (see p 1039)

Rare Tumors.—Rare tumors include leiomyomas of the ciliary body and iris Fig 1109), pigmented and nonpigmented neuroepitheliomas of the iris, ciliary body and retinal pigment epithelium (Figs. 1110-1112) and the diktyoma (a choristomatous tumor of the iris and ciliary body) (Fig 1113)



Fig 1112.—This highly invasive pleomorphic neuroepitheliomatous neoplasm (also called medulloepithelioma) invaded the orbit of a 13-year-old boy H. and E. stain. (×115) (AFIP Acc. 846123) (Courtesy Dr S de Buen.)

TECHNIQUE FOR EXAMINATION AND OPENING OF ENUCLEATED EYES

It is very important that the eye be fixed well oriented properly examined with the aid of a dissecting microscope and transilluminated before it is opened Good fixation is obtained by placing the intact surgical specimen in a pint of 10 per cent aqueous formalin. It is not necessary to open the eye to cut windows into the sclera, or to inject formalin into the vitreous in order to obtain good fixa tion for routine histopathologic techniques. After twenty four hours in formalin the globe should be washed in running tap water for several hours and then placed in 60 per cent ethyl alcohol Formalin is the fixative of choice because it penetrates readily does not discolor and opacify the ocular tissues, and is generally very satisfactory for most staining procedures.

At the time of gross examination it is imperative that the pathologist have a good summary of the clinical history and the results of ophthalmologic examination.

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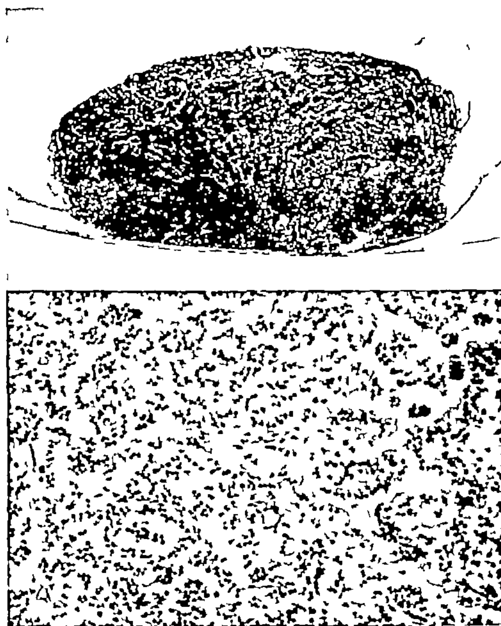


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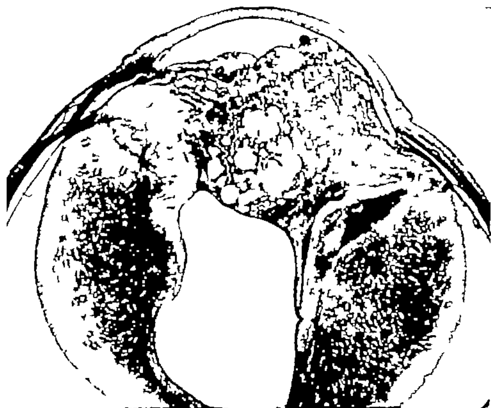
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At the time of gross examination it is imperative that the pathologist have a good summary of the clinical history and the results of ophthalmologic examination.

If there have been accidental or surgical injuries to the globe, their sites should be determined before the eye is opened. Likewise any particular lesion of interest observed in the fundus must be known so that the globe may be advantageously positioned when it is being opened Every effort should be made to open the eye in such a way that the plane of section will include the cornea, pupil lens, and optic nerve along with the lesion of principal clinical interest. If there is no focal lesion that requires a particular plane of section, the horizontal plane is used in order to obtain the macula in the block.



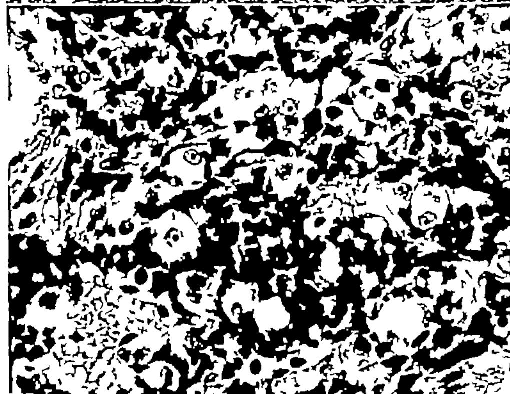
A.

Fig 1113 —The diktyoma or teratoneuroma is a choristomatous neoplasm which usually arises from the region of the iris and ciliary body *A* The large pale-staining lobulated areas in the center of the tumor are masses of hyaline cartilage, shown in greater magnification in *B* H and E. stain (×6) *B* Islands of cartilage are surrounded by sheets of undifferentiated cells, presumably of neurectodermal derivation H. and E. stain. (×115) *C* Ganglion cells are also present in this tumor H and E. stain. (×500) (AFIP Acc. 521152)

Many minute lesions of interest that would ordinarily be overlooked with the naked eye can be detected if the ×7 objective of a binocular dissecting microscope is used. Likewise transillumination of the globe before it is opened will frequently reveal discrete shadows or areas of increased translucency A substage microscope lamp in a darkened room is very satisfactory for this purpose Rotation of the globe over the light source will often reveal in sharp outline the presence of intraocular tumors Such shadows should then be delineated on the sclera with an indelible pencil.

B





C

(Fig 1113 continued)

When the presence of intraocular foreign bodies is suspected it is good practice to x ray the globe before it is opened

The eye is opened with the aid of a double-edged razor blade. During sectioning a right handed individual holds the eye with the left hand, cornea down against the cutting block (Fig 1114) The razor blade is held between the thumb and middle finger of the right hand. With a sawing motion the eye is opened from back to front. The plane of section begins adjacent to the optic nerve and ends through the periphery of the cornea After the interior of the globe is examined a second plane of section, parallel to the first, is made again passing from back to front During this step the eye is placed flat on its cut surface (Fig 1114)

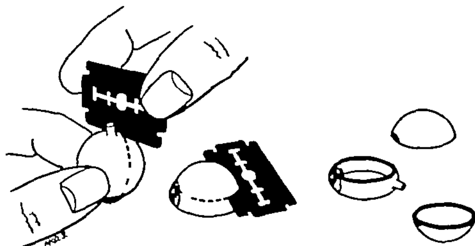


Fig 1114 —Steps used in opening whole eyes. See text for description.

As a result of these two steps a disc-shaped slab about 8 mm. in thickness containing the cornea, pupil lens, and optic nerve is obtained This slab may be carried through the automatic tissue processor along with other surgical specimens that are to be imbedded in paraffin. With experience, excellent paraffin sections may be cut on the rotary microtome though it is technically easier to obtain good histologic preparations with celloidin imbedding and use of a sliding microtome.

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INDEX

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R

S